

# EXHIBIT A



US009040074B2

(12) **United States Patent**  
**Holzer et al.**

(10) **Patent No.:** **US 9,040,074 B2**  
(45) **Date of Patent:** **May 26, 2015**

(54) **MATERIAL AND METHOD FOR TREATING  
INTERNAL CAVITIES**

(2013.01); **A61K 47/10** (2013.01); **A61K 47/38**  
(2013.01)

(75) Inventors: **Asher Holzer**, Raanana (IL); **Dorit Daniel**, Raanana (IL); **Michael Mullerad**, Tel Aviv (IL); **Jaime De La Zerda**, Haifa (IL); **Uri Shpolansky**, Pardes Hana (IL); **Nadav Malchi**, Pardes Hanna-Karkur (IL); **Yosh Dollberg**, Raanana (IL); **Dor Tal**, Hadera (IL); **Yossi Yavin**, Mikhmoret (IL); **Marina Konorty**, Hertzyla (IL)

(58) **Field of Classification Search**

CPC ..... **A61K 9/0024**  
USPC ..... **424/426, 434**  
See application file for complete search history.

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Primary Examiner — Jake Vu

(74) *Attorney, Agent, or Firm* — JMB Davis Ben-David

(57) **ABSTRACT**

A hydrophilic biocompatible sustained-release material is disclosed. The material comprises amounts of Pluronic F-127, PEG-400, HPMC and water, effective to produce a composition of sufficiently low viscosity at room temperature to be injectable into an internal body cavity via a tube inserted within a urinary catheter. At body temperature, the material exhibits a much higher viscosity and will stably adhere to the internal surface of a body cavity. As the material dissolves, a therapeutic agent incorporated therein is slowly released to the body cavity, while the material itself is excreted from the body.

**22 Claims, 8 Drawing Sheets**

(73) Assignee: **Theracoat Ltd.**, Ra'anana (IL)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/553,198**

(22) Filed: **Jul. 19, 2012**

(65) **Prior Publication Data**

US 2013/0046275 A1 Feb. 21, 2013

**Related U.S. Application Data**

(63) Continuation-in-part of application No. PCT/IL2011/000069, filed on Jan. 20, 2011.

(60) Provisional application No. 61/296,589, filed on Jan. 20, 2010, provisional application No. 61/509,654, filed on Jul. 20, 2011.

(51) **Int. Cl.**

**A61K 47/34** (2006.01)

**A61K 9/00** (2006.01)

**A61K 9/06** (2006.01)

**A61K 47/10** (2006.01)

**A61K 47/38** (2006.01)

(52) **U.S. Cl.**

CPC ..... **A61K 9/0034** (2013.01); **A61K 9/0024**  
(2013.01); **A61K 9/006** (2013.01); **A61K 9/06**

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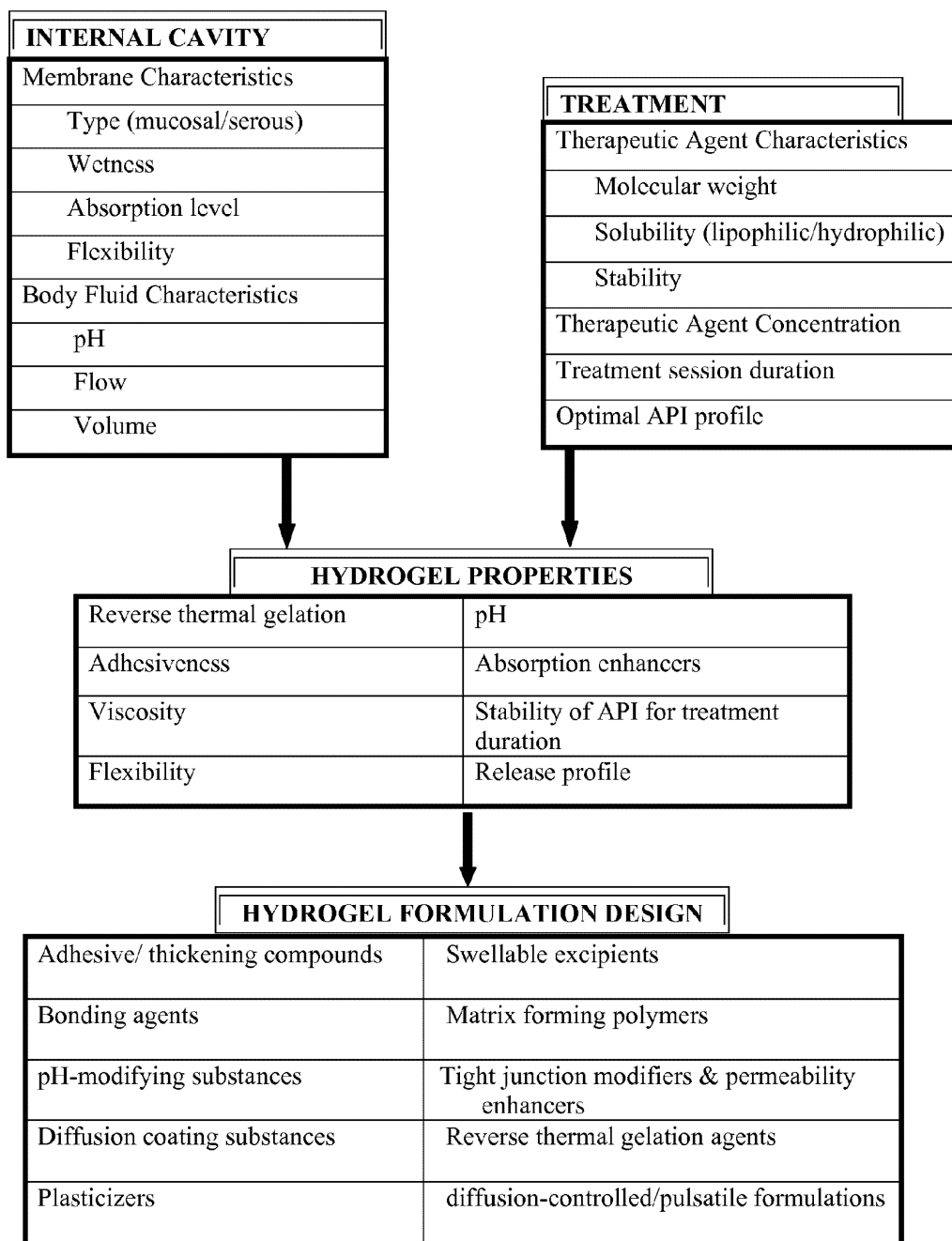


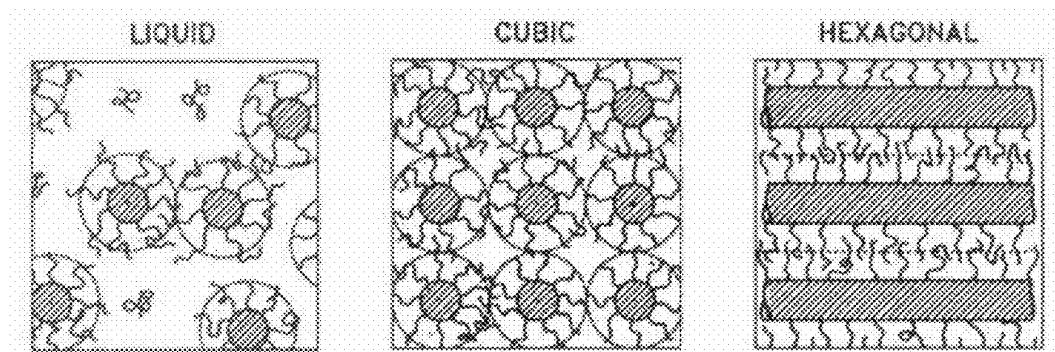
FIG. 1

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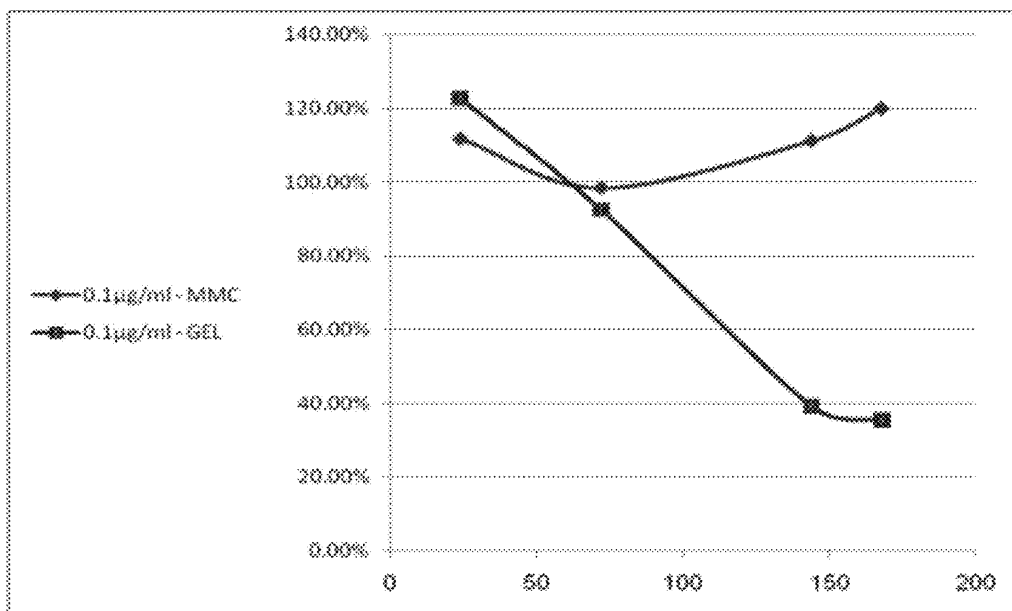
**FIG. 2**  
**(prior art)**

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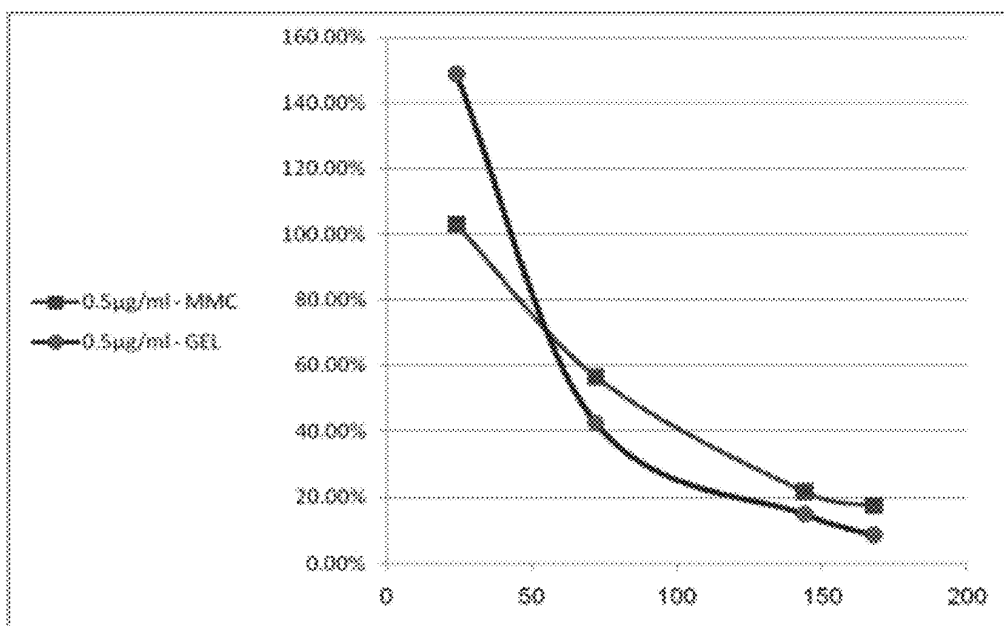
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**FIG. 3A**



**FIG. 3B**

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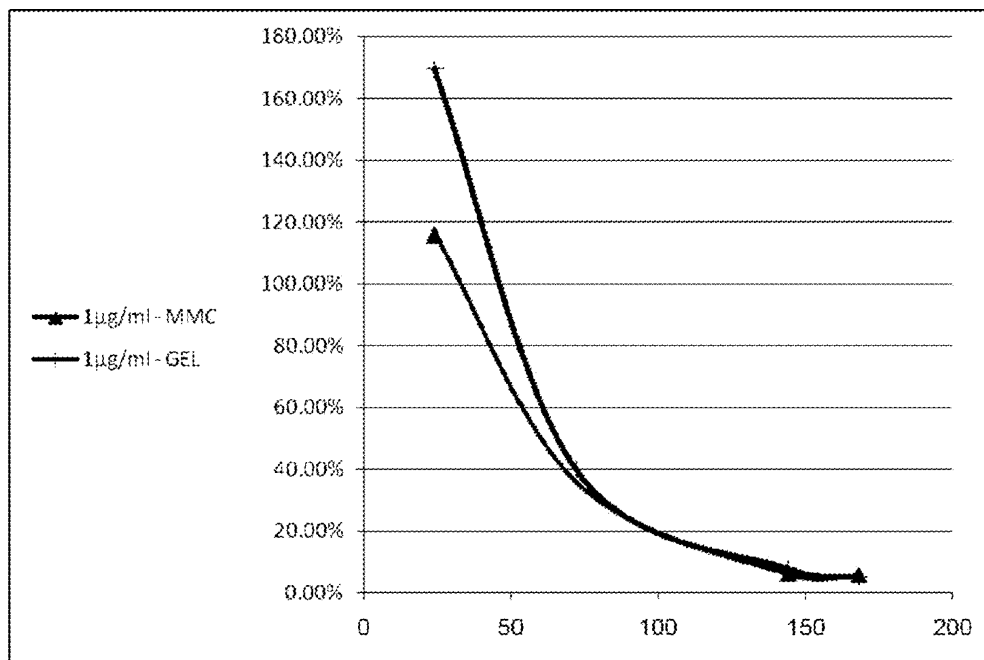


FIG. 3C

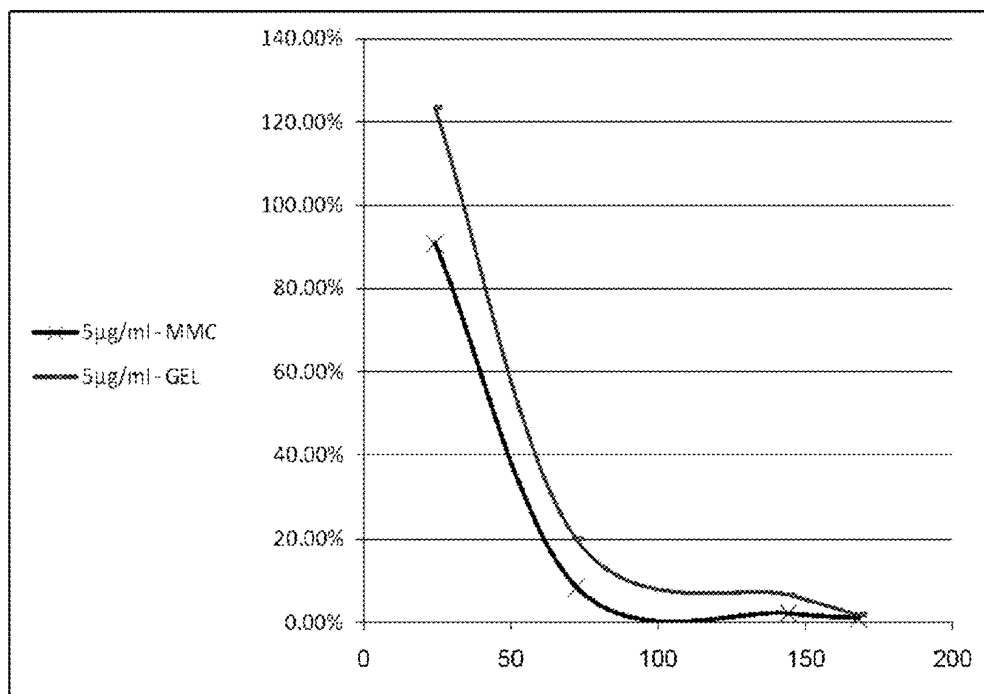


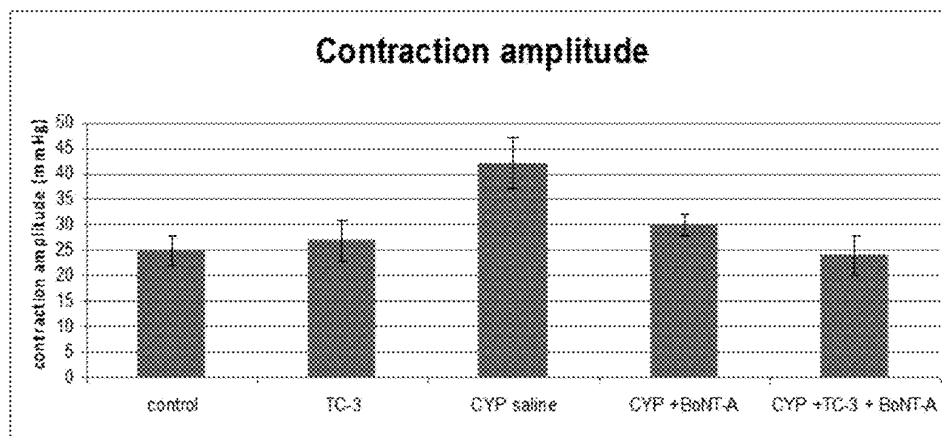
FIG. 3D

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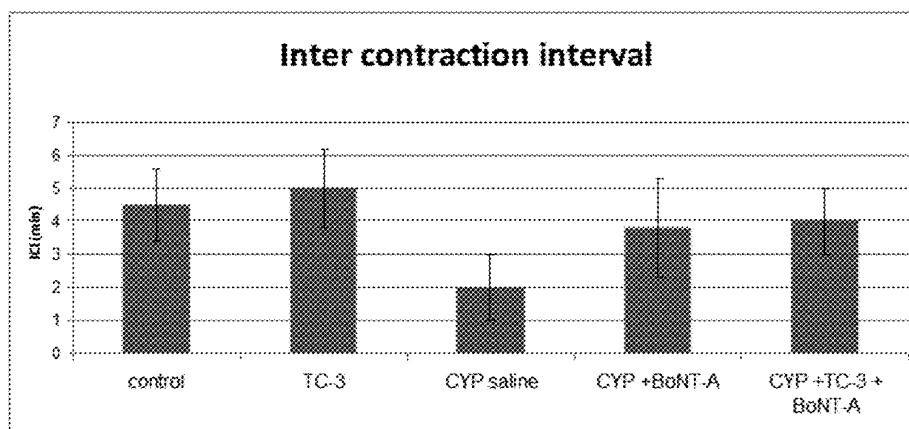
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**FIG 4A**



**FIG 4B**

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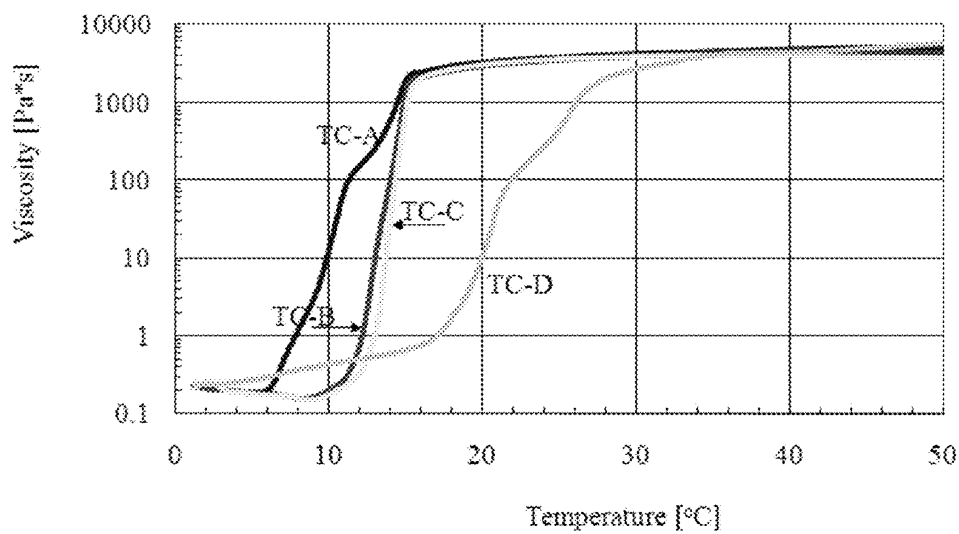


FIG. 5A

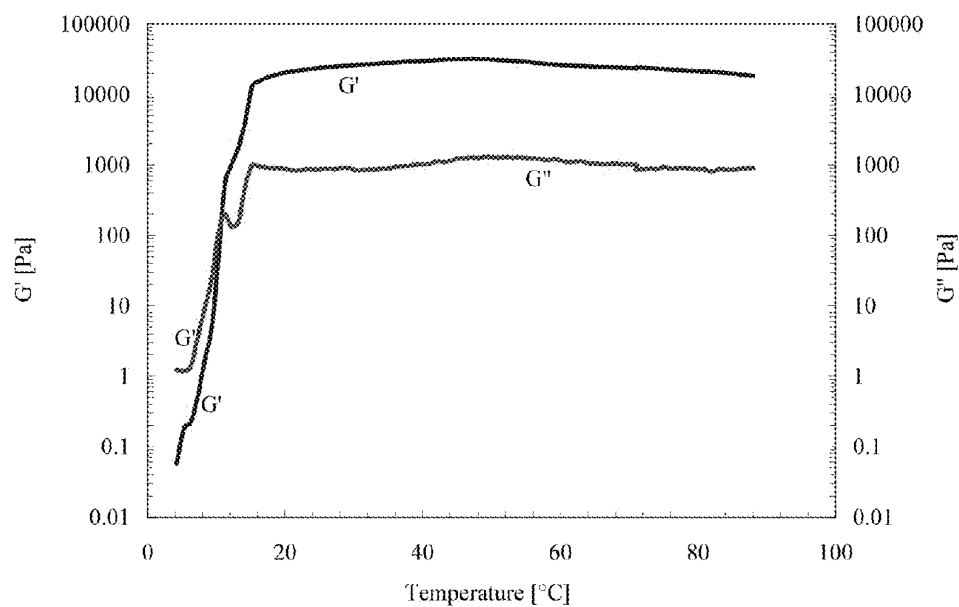


FIG. 5B



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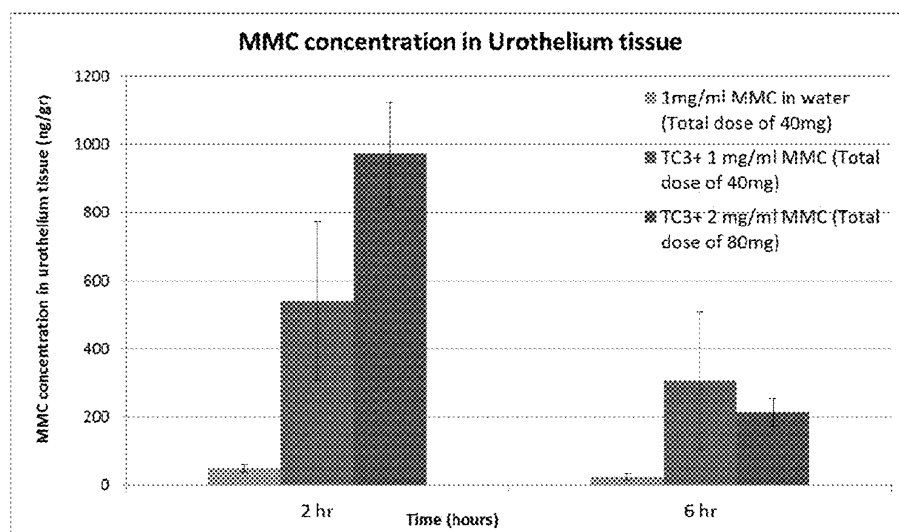


FIG. 6

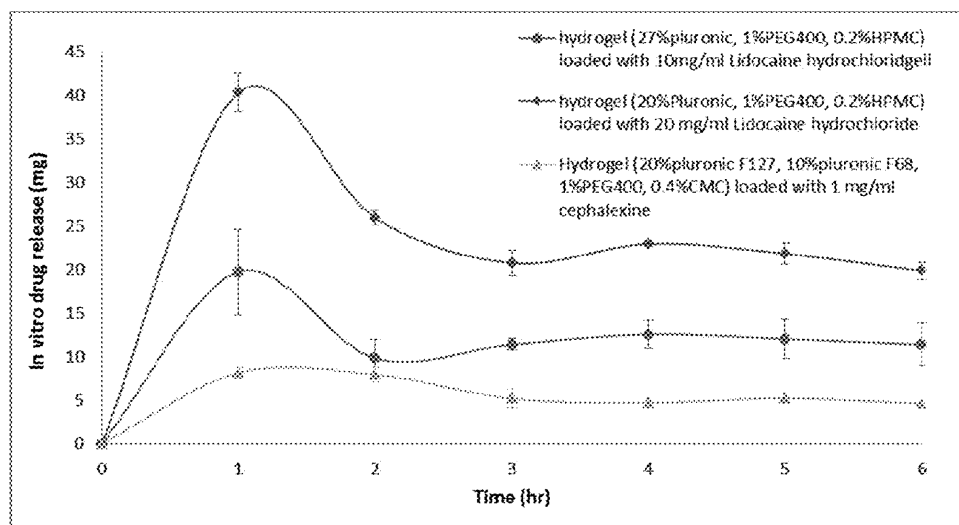


FIG. 7

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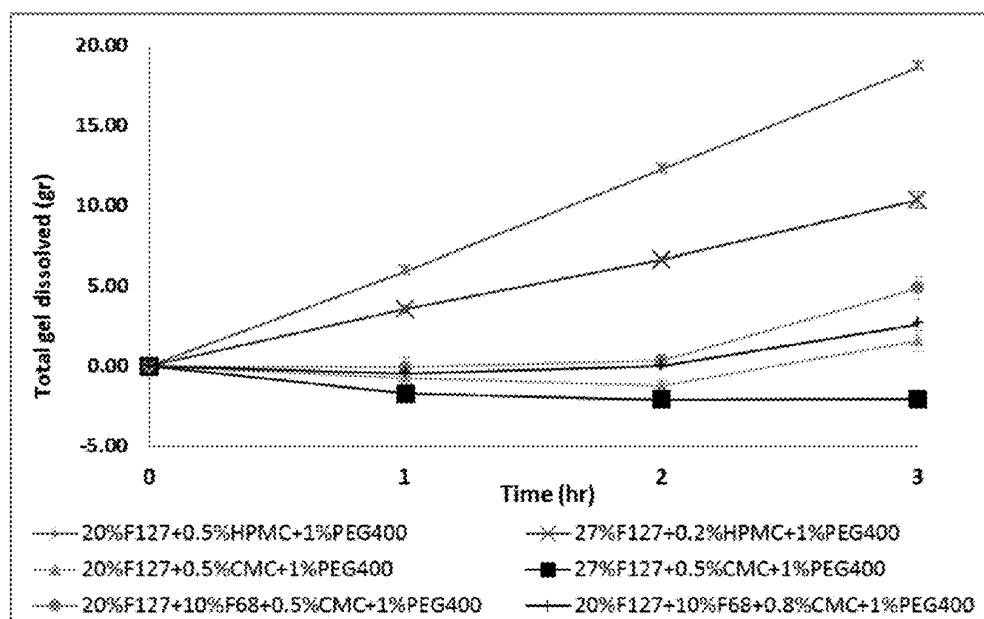


FIG. 8

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**MATERIAL AND METHOD FOR TREATING  
INTERNAL CAVITIES**

## REFERENCE TO RELATED APPLICATIONS

This application is a Continuation-in-Part of International (PCT) Patent Application No. PCT/IL2011/000069, filed 20 Jan. 2011, and claims priority from U.S. Provisional Patent Application No. 61/296,589, filed 20 Jan. 2010. This application also claims priority from U.S. Provisional Patent Application 61/509,654, filed 20 Jul. 2011, all of which applications are hereby incorporated by reference in their entirety.

## FIELD OF THE INVENTION

The invention relates in general to materials, means and methods for sustained release of therapeutic agents for topical treatments. It relates in particular to means and methods for topical treatment of diseases of internal body cavities by embedding therapeutic agents in a slowly degrading biocompatible mixture applied to affected tissue.

## BACKGROUND OF THE INVENTION

## i. Internal Cavities

Internal body cavities (e.g., cavities within the body accessible through a body orifice or via image guided laparoscopic methods) contain organs that when diseased may benefit from prolonged topical exposure to certain drugs. These cavities are naturally wet and are either continuously flushed or generate a flow of body fluids, such as urine, serous fluids or lymphatic fluids—that contribute to gradual expelling of treatment materials.

Many cavities are characterized by their internal natural movement—due, for example, to body motion or peristaltic motion—that constantly changes their shape.

The tissue in all internal cavities in the body is composed of only three basic types of tissue: epithelial, connective and muscular. Almost all epithelial cells, rest on connective tissue, the lamina propria, which support the epithelium and provides nutrition and binds to neighboring structures. The common types of covering epithelia can have either simple, pseudo-stratified or stratified cell structure. The epithelia of vessels and serous cavities are squamous, but many other cavities have epithelia cell structure that is either cuboidal or columnar, which provide good mechanical protection and good ability to achieve adhesion. The mouth, esophagus, larynx, vagina and anal canal have a non-keratinized cell structure to maintain wetness and are more challenging for adhesion. The urinary tract has similar, but transitional cell structure, that provides stretching, mechanical strength and strongest resistance to adhesion of materials.

Several common tissue properties affect the requirements for targeted delivery materials:

- wetness of the cavity lining tissue
- mechanical composition and consistency
- absorption capability
- expansion and movement characteristics of the internal cavities or attached organs
- existence of body fluids for expelling the delivery materials

## ii. Topical Treatment of Diseases

The method by which a drug is delivered can have a significant effect on its efficacy. In many cases, the drug is introduced into the blood system, which then delivers it via the blood stream throughout the body. This form of access is broadly termed systemic treatment. In other cases, a more targeted delivery can focus the therapeutic effect onto the

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target organ, providing therapeutic benefits and avoiding side effects. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. In the context of the present invention, treatments that effect specific tissues or organs by directly accessing them are termed topical treatments, as opposed to systemic treatments that were described above. Sustained release of a drug involves polymers that typically release the drug at a controlled rate due to diffusion out of the polymer or by dilution of the polymer over time. Topical administration of drugs changes the rate at which drugs enter the tissue and the pharmacokinetics of the drug, thus the correctly designed materials can optimize the therapeutic effect by controlling the drug release rate. Since all internal organ tissue is water-based, administering drugs in water-based solutions is optimal.

## iii. Topically Administered Drugs

Among the drugs that can be administered topically are drugs that belong to the following families:

1. Antineoplastic drugs
2. Chemotherapeutic agents
3. Anti-infective agents (e.g. Antimicrobial drugs, Antiparasitic agents, Antivirals)
4. Genito-urinary system drugs
5. Anti-inflammatory products
6. Analgesics
7. Musculoskeletal system acting drugs
8. Drugs acting on the blood and blood forming organs (Antihemorrhagics, Antithrombotic agents, antianemic drugs)
9. Dermatologic drugs (antifungals, antiseptic)
10. Gastrointestinal system (antiobesity, acid related disorders)
11. Metabolism drugs
12. Neurological drugs
13. Respiratory drugs including nasal drugs
14. Cardio-vascular drugs
15. Otological drugs
16. Anti-infective drugs
17. Corticosteroids drugs
18. Analgesics drugs
19. Antiparasitics drugs
20. Anesthetic Drugs

In other cases, the topical treatment is just evolving:

21. Growth factor (e.g., for treatment of heart muscle ischemia)
22. Gene Therapy agents

In other cases, the topically administered material has medical effect without actually being considered an active pharmaceutical ingredient:

23. Mucin
24. Hyaluronic Acid

Besides their therapeutic effect, drugs are classified according to their chemical and physical properties and thus constitute families of compounds that, due to their common similar characteristics, fit particular drug vehicles. Some of those properties include:

- Lipophilicity or hydrophilicity
- Molecular weight and physical size
- Diffusability through different media which is hydrophobic, hydrophilic, viscose, etc.
- Solubility

## iv. Physical characteristics of internal cavities

The effectiveness of application of a topical therapeutic agent to a specific internal cavity will depend on the physical

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characteristics of the inner tissue of that internal cavity, in particular, characteristics such as:

Access—ease of introducing liquid or gel into the cavity

Tissue type that defines adhesiveness—ability to attach reliably and consistently polymer to the cavity tissue

Internal movement—effected by gravitational motion, stretching, peristaltic motion, etc. that cause periodical changes in the shape and volume of the cavity—pressure and volume regime

Wetness—to enable diffusion of drugs into the tissue

Degradability mechanism—flow of liquids or aqueous solutions, e.g. urine, serous or lymphatic fluids,

The specific values of cavity characteristics require careful consideration in the development of topical drugs suitable for treatment of diseases inside these cavities.

Table 1 summarizes the different organs, types of tissue their inner lining is made of and characteristics of the surrounding medium.

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In the particular case of treatment of bladder cancer, the bladder tissue penetration by chemotherapy drugs—a critical parameter in treatment effectiveness—exhibits a linear relationship with the concentration of the chemotherapy drugs (see Gao X, Au J L, Badalament R A, Wientjes M G. Bladder tissue uptake of mitomycin C during intravesical therapy is linear with drug concentration in urine. Clin Cancer Res. 1998 January; 4(1):139-43)). Furthermore, chemotherapy drug penetration is 40% higher in the tumor tissue than in the adjacent normal urothelium. Gao et al demonstrated double Mitomycin C (MMC) concentration in tissue when installing 40 mg/20 ml as compared with 20 mg/20 ml MMC: human bladder tumors had a significantly higher tissue uptake of MMC than the normal bladder tissue.

The anti-tumor effect of chemotherapy drugs depends on concentration and exposure time. Schmittgen et al (see Schmittgen T D, Wientjes M G, Badalament R A, Au J L.

TABLE 1

System	Organ	Type of Tissue	Elasticity/ Mobility	pH	Surroundings
Digestive	Mouth/Tongue	Mucosal	Very	Neutral	Flow of food and liquids
	Esophagus	Mucosal	None	Neutral	Flow of food and liquids
	Stomach	Mucosal	Very	Strongly acidic	Very acidic fluids, enzymatic activity
	Duodenum	Mucosal	Moderate	Slightly alkaline	Flow of bolus, enzymatic activity
	Small intestine	Mucosal, ciliated	Moderate	Slightly alkaline	Flow of bolus, enzymatic activity, absorption of nutrients
	Large intestine	Mucosal	Moderate	Slightly alkaline	Flow of feces
	Rectum	Mucosal	Moderate	Slightly alkaline	Flow of feces
Respiratory	Mouth/Nose	Mucosal	None	Neutral	Flow of air and humidity
	Larinx	Mucosal	Moderate	Neutral	Flow of air and humidity
	Eustachian tubes	Mucosal, ciliated	None	Neutral	Presence of air, humidity
	Pharinx	Mucosal	Moderate	Neutral	Flow of air and humidity
	Trachea	Mucosal	None	Neutral	Flow of air and humidity
	Lungs/Alveoli	Mucosal	Moderate	Neutral	Flow of air and humidity
Urinary	Kidneys	Mucosal	None	Slightly acidic	Blood filtration, production of urine
	Ureters	Mucosal	None	Slightly acidic	Flow of urine
	Bladder	Mucosal	Very	Slightly acidic	Accumulation and evacuation of urine
	Prostate	Mucosal	None	Slightly acidic	Flow of urine and semen (slightly alkaline in ejaculation)
	Urethra	Mucosal	Moderate	Slightly acidic	Flow of urine and semen (in the males)
Genital	Vas deferens	Mucosal, ciliated	None	Neutral	Flow of seminal fluids
	Epididymis	Mucosal, ciliated	None	Neutral	Flow of seminal fluids
	Testes	Mucosal	Moderate	Neutral	Production of seminal fluids
	Vagina	Mucosal	None	Neutral	Coitus, flow of semen, flow of menstrual fluids
	Cervix	Mucosal	Moderate	Neutral	Flow of semen, flow of menstrual fluids
	Fallopian tubes	Mucosal, ciliated	None	Neutral	Flow of semen, flow of menstrual fluids
Pleura	Ovules	Mucosal	None	Neutral	Production of ova
	Pleural membranes	Serous	Moderate	Neutral	Pleural fluids
Peritoneum	Peritoneal membranes	Serous	Moderate	Neutral	Peritoneal fluids

#### v. Chemotherapy—Anticancer Drugs

Many chemotherapy (antineoplastic) drugs used as cancer treatments bind to DNA, resulting in synthesis inhibition and strand breakage. In standard intravesical instillations, chemotherapy drugs are administered at dose concentrations of around 1 mg/ml for 1-2 hour sessions.

Pharmacodynamics of mitomycin C in cultured human bladder tumors. Cancer Res. 1991 Aug. 1; 51(15):3849-56) demonstrated, both in TCC cell cultures and human bladder tumor tissue cultures, that a ten times higher concentration was needed in order to get a similar cell kill effect when exposure time to MMC was reduced from 24 hours to two hours.

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The proven conclusion is that maintaining higher drug concentration for longer treatment duration will enhance the treatment efficacy.

#### vi. Required Properties for Topical Treatment in the Bladder and Other Internal Cavities

One approach to treatment of diseases of internal body cavities such as the bladder is topical application of a therapeutic agent entrained in a suitable matrix/mixture. The properties of the materials to be used in such a matrix/mixture must be adapted to the needed medical effect.

Important properties include:

Rheological properties (viscosity, thixotropy,  $G'$ ,  $G''$ )—required for the introduction of the material into the internal cavity

Adhesion—required to coat dependably the target tissue

Flexibility—to comply with the volume and shape natural changes of the internal cavity under treatment

Dilution in aqueous solution—to enable API release and natural expelling of the material through body fluids

Mechanical properties, such as hardness, tensile strength to provide

Duration of time that the material remains in the internal cavity before it degrades

A suitable Active Pharmaceutical Ingredient (API)—the medical drug or drug derivative chosen from the families listed in section iii

Loading of drug or API in the material. For certain clinical protocol the amount and concentration of the drug or API mixed into the material have to be set to a prescribed level. The amount of therapeutic agent thus used can be significantly lower than used in regular parallel instillations and more than a single API can be loaded. So the API part of the administered material may vary from zero concentration (gel only) to 50% (e.g., for DMSO).

The ability of the matrix/mixture to release the drug in a controlled manner such that the actual drug concentration vis-à-vis the organ tissue or lining upon which the mixture is adhered will be optimal for each treatment. It is precisely the specific composition of the mixture that determines the release profile of the drug and its adsorption into the target tissue. For example, if the API is lipophilic, the addition of certain surface-active agents in given concentrations will provide for their emulsification, easier release from the drug composition and easier absorption by the internal organ lining.

Drug viability. The material is designed and tested not to reduce the viability duration of the drug or API that is mixed into it, so that the amount that is released throughout the treatment will have the optimal therapeutic effect.

#### vii. Limitations of Superficial Bladder Cancer (SBC) Treatments Known in the Art

SBC is a highly-recurrent form of cancer. To lower recurrence, it is considered necessary to treat patients with a single intravesical chemotherapy instillation immediately after TUR-T.

A meta-analysis of 7 randomized trials (1,476 patients with a median follow-up of 3.4 years) has demonstrated that one chemotherapy instillation immediately after Tumor resection (TUR) decreases the relative risk of recurrence by 40% (see Sylvester R J, Oosterlinck W, van der Meijden A P. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol.* 2004 June; 171(6 Pt 1):2186-90). The timing of the instillation is crucial: in all studies, instillation was administered within 24 hours. A study

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reported that if the first instillation was not given within 24 hours, the risk of recurrence increased twofold (see Kaasinen E, Rintala E, Hellström P, Viitanen J, Juusela H, Rajala P, Korhonen H, Liukkonen T; FinnBladder Group. Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma. *Eur Urol.* 2002 August; 42(2):167-74).

Following resection and first immediate treatment patients need to be stratified by their risk for tumor progression and recurrence:

Patients with low risk for disease progression/recurrence (30%)—need no further instillations.

Intermediate risk patients (40-50%)—usually receive 6 additional sessions of Mitomycin C (MMC) chemotherapy instillations.

High risk patients (20%)—are treated with 6 intravesical Bacillus Calmette-Guerin (BCG) instillations.

The efficacy of the current standard topical chemotherapy treatment for Superficial Bladder Cancer (intravesical instillation) is limited, because there is no control on the chemotherapy concentration and the time until it is expelled. In an attempt to prolong the standard treatment to two hours, some physicians dictate behavioral conditions to reduce acidity of the bladder, to reduce the volume of urine before the instillation and instill maximal concentration of chemotherapy dissolved in minimal volume of saline.

There are several obstacles and complications known that accompany the presently used methods for coating the internal wall of the bladder (and hence for topical treatments for bladder cancer):

The mucosal membrane. One of the physiological purposes of the mucosal membrane that covers the bladder's inner wall, which is permanently soaked in urine (i.e., a watery composition), is to prevent adherence of foreign bodies to it. Therefore, any composition targeted to adhere to the internal wall of the bladder will have to overcome the difficulty of adhering to such mucosal membrane. Furthermore, since the mucosal layer is in constant contact with urine, in order to coat it, a hypothetical option would be to initially dry it. However, such an operation is not acceptable in present medical practice. Another complication stems from the membrane structure, which is composed from several cell layers where the outermost is the terminally differentiated 'umbrella' cells that are the urothelium most superficial layer. Regular biological adhesives, such that are used to stop bleeding (e.g. Tabotamp that is distributed by Johnson & Johnson, NJ, USA), can bond strongly through the wet surface and peel-off that delicate, outermost layer and thus damage the membrane. The achievement of a satisfactory non-damaging coating of wet, non-adherent mucosal tissue is very challenging indeed.

The bladder's natural expansion and collapse. The bladder is essentially muscular tissue and its wall is naturally highly flexible. The inner volume of a mature bladder varies greatly, from a collapsed or 'empty' state with a volume of 0-30 ml up to a filled bladder with a volume of up to 500-600 ml (though the bladder usually fills only up to 150-200 ml before micturition point, that is, when the individual feels the urge to urinate and indeed vacates the bladder. Therefore, providing a composition that has the capacity to adhere and conform to the bladder wall without damaging the outer layer, adapt itself to the bladder's morphology in spite of the great variance



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in volume and the fact that it is permanently changing its form and volume and stay adhered to it is considered an enormous challenge.

Further to the above mentioned difficulties to adhere onto a mucosal membrane, it is also highly challenging to do so while avoiding the peeling-off of the outermost layer of the membrane—due to adhering shear forces or adhesion between tissue areas. So while biological glues that can stop bleeding can also adhere through the wet mucosal layer, their rigidity compromises the integrity of the outermost layer and negates the required therapeutic effect.

The same obstacles, to even greater extent, are relevant to the treatment of the same cancer (transitional cell carcinoma) in the upper urinary tract. TCC in the upper urinary tract is a rare urological disease and has a propensity for multifocality, local recurrence, and development of metastases. Almost 5% of all urothelial neoplasms occur in the kidney and ureters. The standard treatment for patients with upper tract TCC and a normal kidney is a complete removal of the involved kidney, ureter and bladder cuff. A less-invasive treatment, namely resection of tumors followed by instillation with chemotherapy or immunotherapy, is recommended for patients with anatomic or functional solitary kidneys, bilateral upper-tract TCC, base line renal insufficiency, or inability to tolerate major surgery. Patients with a normal contralateral kidney who have small, low-grade lesions can also be reasonable candidates for this organ conserving management.

Topical immunotherapy or chemotherapy instillations for treatment of UTUC are used as primary or adjuvant treatment in order to reduce tumor recurrence. Topical instillation is performed using either infusion through a percutaneous nephrostomy tube, via a retrograde ureteral catheter, or by retrograde reflux from the bladder with an indwelling double-J stent. The main disadvantage in all these treatments is the short residual duration of the active agent in the treated area resulting in a low exposure time essential for treatment efficacy. This may be one of the reasons for the shorter average disease-free duration of upper tract TCC patients, compared to lower tract TCC patients.

Another bladder disease is overactive bladder (OAB)—when the bladder contracts suddenly without patient's control when the bladder is not full. This syndrome affects an estimated 1 in 11 adults in the United States—especially common in older adults.

Current available treatment options for OAB are: bladder training, pelvic floor exercises, drug therapy such as anti-cholinergics, capsaicin, intravesical botulinum toxin injections and in severe cases—bladder augmentation surgery.

Current oral drugs have high adverse event rate which leads to patients' intolerance. Bladder instillation with antimuscarines has been tried with lower adverse event rate, but require recurrent catheterization due to the drug relatively short half-life that reduces compliance.

Despite promising results the drawbacks to intravesical botulinum toxin injections are numerous: the cystoscopic injection requires proficiency and authorization of the physician, some degree of anesthetic administration is required, the botulinum toxin effects only the injected anatomical locations and the treatment may lead to temporary urinary retention and need for self-catheterization.

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viii. Mechanical Support and Sustained Drug Release in Minimally-Invasive Surgery

The limited number of access ports used in laparoscopic surgery may impair the ability of the surgeon to achieve adequate retraction and exposure, or to stabilize “moving targets” while operating on nonfixed organs. Current solutions include adding more ports or using a hand-assisted technique—which have the disadvantages of being more invasive, possibly creating a cumbersome situation of multiple instruments in a limited working space—or the use of temporary sutures that pass through the abdominal wall.

The current invention provides means by which the organs can be held mechanically in place by injecting the invented materials into the cavity and letting them to solidify and support the internal organs. This invented materials and method have the additional advantages of a) serving as a soothing dressing for the surgery cuts, b) contribution to healing through sustained release of anti-infection drug and analgesic drug for a therapeutically-significant duration (e.g., over 6 hours), and c) avoiding the need for further surgical or medical procedure, by natural degradation of the material and its expelling from the body.

Similar method, but with a different family of materials can be used to prevent the adhesion of tissues between organs in the treated area, which may often occur during laparoscopic surgery.

ix. Current State-of-the-Art

To the best of the inventors' knowledge, a method for treating diseases of the bladder or other inner cavities based on production of a solidified coating layer and affixing it onto the internal wall of the bladder or other cavities, followed by continuous release of the therapeutic agent(s) from the coating, remains unknown in the art.

Furthermore, the application of the substrate material such that it creates a continuous layer substantially affixed to the mucosal lining of the bladder or the outermost tissue of other internal cavity for prolonging the exposure of the drug to the targeted cells is neither trivial nor obvious to any person skilled in the art.

Compositions known in the prior art as sustained-release substrates for the treatment of bladder cancer (for example, the invention disclosed in U.S. Pat. Appl. US2006/0127420 to Chung) are lipophilic (oil-based). Given that the inner bladder wall is mucosal, essentially and permanently soaked in an aqueous medium (i.e., urine), a drug embedded in a hydrophilic medium would more effectively diffuse through the matrix/mixture and conveniently reach the bladder wall, allowing in that way an intimate, continuous contact between the drug and the bladder wall.

Thus, there remains a long-felt and unmet need for a material with the following properties: it is hydrophilic; it provides a homogeneous layer that can securely adhere to the surfaces of internal body cavities, in particular, mucosal tissue of such cavities as the bladder; it remains attached despite the natural motions of the tissue to which it is attached; it is easily applied; it is biocompatible; it provides a continuous sustained release of a therapeutic agent; the rate of release of the therapeutic agent is determined by the concentration of the agent and the rate of degradation of the material; and after the material degrades, it is excreted from the body by the body's own natural processes.

#### SUMMARY OF THE INVENTION

The current invention is designed to answer this long-felt need. It comprises a series of systems that combine therapeutic materials and application means for the topical treatment

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of diseases that are focused in internal cavities, such as a system for treating Superficial Bladder Cancer (SBC).

It is therefore an object of the present invention to disclose the use of a thermoreversible hydrogel composition in a system for delivery of a therapeutic agent to the urinary tract, characterized in that said thermoreversible hydrogel composition comprises a thermoreversible hydrogel characterized by: a viscosity of less than 200 Pa·s over a temperature range of 4° C.-12° C.; a viscosity of greater than 10<sup>3</sup> Pa·s at 37° C.; a “peel strength” adhesiveness according to ASTM standard D2256-03 of 0.5-5.0 N cm<sup>-2</sup> at 37° C.; and, flexibility sufficient such that a 3 cm<sup>2</sup>×3 cm<sup>2</sup> section of bladder tissue layered with said thermoreversible hydrogel at room temperature can be stretched to 9 cm<sup>2</sup>×9 cm<sup>2</sup> without detachment of said thermoreversible hydrogel from said bladder tissue.

It is a further object of this invention to disclose such a use of a thermoreversible hydrogel composition in a system for delivery of a therapeutic agent to the urinary tract, wherein said composition additionally comprises an effective amount of at least one therapeutic agent for treatment of the urinary tract.

It is a further object of this invention to disclose the use of a hydrogel composition in a system for delivery of a therapeutic agent to the pleura, characterized in that said hydrogel composition comprises a thermoreversible hydrogel characterized by a viscosity of less than 5 Pa·s over a temperature range of 4° C.-12° C.; a viscosity of greater than 10<sup>3</sup> Pa·s at 37° C.; a “peel strength” adhesiveness according to ASTM standard D2256-03 of 0.5-5.0 N cm<sup>-2</sup> at 37° C.; and flexibility sufficient such that a 3 cm<sup>2</sup>×3 cm<sup>2</sup> section of bladder tissue layered with said thermoreversible hydrogel at room temperature can be stretched to 9 cm<sup>2</sup>×9 cm<sup>2</sup> without detachment of said thermoreversible hydrogel from said bladder tissue.

It is a further object of this invention to disclose the use of a hydrogel composition in a system for delivery of a therapeutic agent to the pleura, wherein said composition additionally comprises an effective amount of a therapeutic agent for treatment of the pleura.

It is a further object of this invention to disclose the use of a thermoreversible hydrogel composition in a system for delivery of a therapeutic agent to a mucosal or serous membrane, characterized in that said hydrogel composition comprises a thermoreversible hydrogel characterized by a viscosity of less than 5 Pa·s over a temperature range of 4° C.-12° C.; a viscosity of greater than 10<sup>3</sup> Pa·s at 37° C.; a “peel strength” adhesiveness according to ASTM standard D2256-03 of 0.5-5.0 N cm<sup>-2</sup> at 37° C.; and flexibility sufficient such that a 3 cm<sup>2</sup>×3 cm<sup>2</sup> section of bladder tissue layered with said thermoreversible hydrogel at room temperature can be stretched to 9 cm<sup>2</sup>×9 cm<sup>2</sup> without detachment of said thermoreversible hydrogel from said bladder tissue.

It is a further object of this invention to disclose such a use of a thermoreversible hydrogel composition in a system for delivery of a therapeutic agent to a mucosal or serous membrane, wherein said composition additionally comprises an effective amount of a therapeutic agent for treatment of a mucosal or serous membrane.

It is a further object of this invention to disclose such a use of a thermoreversible hydrogel composition in a system for delivery of a therapeutic agent to a mucosal or serous membrane, wherein said mucosal or serous membrane is located at an internal cavity chosen from the group consisting of, mouth, nasal sinus, paranasal sinus, gallbladder, esophagus, rectum, lungs, vagina, uterus, stomach, renal pelvis, pleura, abdomen, peritoneum, pelvis, liver, kidney, heart, intestine, brain, and vertebral column.

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In some embodiments of the invention, said thermoreversible hydrogel is further characterized by a viscosity of less than 5 Pa·s over a temperature range of 4° C.-12° C. In some embodiments of the invention, the said thermoreversible hydrogel is further characterized by a viscosity of less than 0.5 Pa·s over a temperature range of 4° C.-12° C. In some embodiments of the invention, the thermoreversible hydrogel is further characterized by a viscosity of greater than 3×10<sup>3</sup> at 37° C.

In some embodiments of the invention, said thermoreversible hydrogel has a “peel strength” adhesiveness according to ASTM standard D2256-03 of 1.0-5.0 N cm<sup>-2</sup> at 37° C.

In some embodiments of the invention, said thermoreversible hydrogel is additionally characterized by flexibility sufficient to permit the volume of the tissue to which said composition is applied to expand by a factor of at least 3 without detachment of said gel from said tissue.

In some embodiments of the invention, said thermoreversible hydrogel comprises between 20% and 30% (w/w) ethylene oxide/propylene oxide block copolymer; between 0.05% and 0.5% (w/w) hydroxypropylmethylcellulose (HPMC); between 0.1% and 2.5% (w/w) polyethylene glycol (PEG)-400; and the balance water.

In some embodiments of the invention, said thermoreversible hydrogel comprises between 20% and 30% (w/w) ethylene oxide/propylene oxide block copolymer; between 0.1% and 0.3% (w/w) HPMC; between 0.1% and 1.8% (w/w) PEG-400; and the balance water.

In some embodiments of the invention, said thermoreversible hydrogel comprises between 18% and 40% (w/w) ethylene oxide/propylene oxide block copolymer; between 0.05% and 0.8% (w/w) CMC; between 0.1% and 2.5% (w/w) PEG-400; and the balance water.

In some embodiments of the invention, said thermoreversible hydrogel comprises between 12-30% Pluronic F127; between 5-30% Pluronic F68; between 0.05% and 2% (w/w) CMC; between 0.1% and 2.5% (w/w) PEG-400; and the balance water.

It is a further object of this invention to disclose such a use as defined in any of the above, wherein said thermoreversible hydrogel additionally comprises at least one component selected from the group consisting of adhesive and thickening compounds; bonding agents; pH-modifying substances; diffusion coatings; plasticizers; components for increasing permeability within the formulation; swellable excipients; matrix forming polymers; tight junction modifiers/cell membrane permeability enhancers; and any combination thereof.

In some embodiments of the invention, said bonding agent is selected from the group consisting of polycarboxylic acid, cellulose, microcrystalline cellulose, cellulose derivatives, HPMC, hydroxypropylcellulose (HPC), low-substituted hydroxypropylcellulose, dicalcium phosphate, lactose, sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), polyvinylpyrrolidone (PVP), vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides, hyaluronic acid, fats, fatty acid derivatives, and any combination thereof.

In some embodiments of the invention, said diffusion coating is chosen from the group consisting of ethylcelluloses and polymethacrylates, cellulose acetate and cellulose acetate butyrate or any combination thereof.

In some embodiments of the invention, said component for increasing permeability within the formulation is chosen from the group consisting of polyethylene glycols, PVP, PVA, HPMC, HPC, hydroxyethylcelluloses (HEC), methylcellu-

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lose (MC), carboxymethylcelluloses and their salts, dextrans, maltodextrins, cyclodextrins, dextrans, urea, salts, sugars, sugar alcohols, and any combination thereof.

In some embodiments of the invention, said swellable excipient is selected from the group consisting of polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, polyethylene oxides, polymethacrylates, L-HPC, cellulose acetate, ethylcellulose, polymethacrylates, high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, poly(hydroxyalkyl methacrylate), alginates, galactomannans, and any combination thereof.

In some embodiments of the invention, said matrix forming polymer is selected from the group consisting of hydroxyethylmethylcelluloses, HPC, HEC, MC, ethylcelluloses, alkylcelluloses, hydroxyalkylcelluloses, hydroxyalkylmethylcelluloses, sodium CMCs, alginates, galactomannans, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives, polyvinyl alcohols, partially hydrolysed polyvinyl acetate, polyvinylpyrrolidone, agar, pectin, gum arabic, tragacanth, gelatin, starch, starch derivatives poly(propylene oxide) (PPO), poly(lactide-co-glycolic acid) (PLGA), poly(N-isopropylacrylamide) (PNIPAM), poly(propylene fumarate) (PPF), polyurethane (PU), poly(organophosphazene) (POP), stearic acid, poly(acrylic acid), glyceryl stearate, cetaryl alcohol, sodium stearyl lactylate, hydroxy-lanolin, and any combination thereof.

In some embodiments of the invention, said tight junction modifier/cell membrane permeability enhancer is chosen from the group consisting of anionic surfactants, non-anionic surfactants, charged polymers, dimethyl sulfoxide (DMSO), decylmethyl sulfoxide, tert-butyl cyclohexanol, fatty acids their esters and salts, ethanol, nicotinamide, urea, perfluoropolyether, monoterpene ketones, disodium citrate, succinic acid and tris.

In some embodiments of the invention, said surfactant is chosen from the group consisting of polysorbates, sodium dodecyl sulfate, and dextran sulfate.

In some embodiments of the invention, said charged polymer is chosen from the group consisting of chitosan poly-arginine, polylysine, and aliginite.

In some embodiments of the invention, said monoterpene ketone is chosen from the group consisting of like (-) menthol, (-) menthone, peppermint oil, and spearmint oil.

In some embodiments of the invention, said thermoreversible hydrogel is additionally used as a biological glue.

It is a further object of this invention to disclose such a use as defined in any of the above, further characterized in that said composition releases said therapeutic agent, over a temperature range of 36° C.-42° C. and a pH range of between 5.5 and 8.0, at a rate of 80% in a time range of between 3 and 30 hours.

It is a further object of this invention to disclose such a use as defined in any of the above, further characterized in that said composition releases said therapeutic agent, over a temperature range of 36° C.-42° C. and a pH range of between 1 and 9.0, at a rate of 80% in a time range of between 3 and 30 hours.

It is a further object of this invention to disclose such a use as defined in any of the above, further characterized in that said composition releases said therapeutic agent, over a tem-

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perature range of 36° C.-42° C. and a pH range of between 1 and 9.0, at a rate of 80% in a time range of between 2 and 4 weeks.

It is a further object of this invention to disclose such a use as defined in any of the above, wherein said therapeutic agent for treatment of the urinary tract is selected from the group consisting of antineoplastic agents, chemotherapeutic agents, anti-infective agents, antimicrobial agents, antiparasitic agents, antiviral agents, agents acting on the blood, antihemorrhagics, antithrombotic agents, antifungals, antiseptics, agents for treating diseases of the genito-urinary system, anti-inflammatory agents, neurological agents, gene therapy agents, corticosteroids, analgesic and anesthetic agents, growth factors, VEGF, inhibitory factors, LIF, proteins, mucin, and any combination thereof.

It is a further object of this invention to disclose such a use as defined in any of the above, wherein said therapeutic agent for treatment of the urinary tract is selected from the group consisting of Mitomycin C, Doxorubicin, Valrubicin, and Gemcitabine, Thiotepe, Ethoglucid (Epodyl), Epirubicin, Pirarubicin, Apaziquone, Vicinium and botulinum toxin, and interleukin-2

It is a further object of this invention to disclose such a use as defined in any of the above, wherein said system further comprises a second hydrogel composition used subsequently, said second hydrogel composition comprising a thermoreversible hydrogel characterized by a viscosity of less than 200 Pa·s over a temperature range of 4° C.-12° C.; a viscosity of greater than 10<sup>3</sup> Pa·s at 37° C.; a "peel strength" adhesiveness according to ASTM standard D2256-03 of 0.5-5.0 N cm<sup>-2</sup> at 37° C.; and flexibility sufficient such that a 3 cm<sup>2</sup>×3 cm<sup>2</sup> section of bladder tissue layered with said thermoreversible hydrogel at room temperature can be stretched to 9 cm<sup>2</sup>×9 cm<sup>2</sup> without detachment of said thermoreversible hydrogel from said bladder tissue; and an effective amount of a cell cycle modifying agent for synchronization of cell cycle chosen from the group consisting of chalcones, colcemid, methotrexate, and thymidine.

It is a further object of this invention to disclose such a use as defined in any of the above, wherein said system is further characterized in that it is designed to release said therapeutic agent continuously for at least 12 hours.

It is a further object of this invention to disclose a method for administering a therapeutic agent to the internal surface of an internal body cavity, comprising:

incorporating an effective amount of said therapeutic agent into a biocompatible sustained-release material chosen from the group consisting of (a) biocompatible sustained-release materials comprising between 20% and 30% (w/w) ethylene oxide/propylene oxide block copolymer, between 0.05% and 0.5% (w/w) HPMC, between 0.1% and 2.5% (w/w) PEG-400, and the balance water; and (b) biocompatible sustained-release materials comprising between 20% and 30% (w/w) ethylene oxide/propylene oxide block copolymer; between 0.1% and 0.3% (w/w) HPMC; between 0.1% and 1.8% (w/w) PEG-400; and the balance water;

inflating a balloon to open said internal body cavity to a substantially symmetrical shape;

introducing said biocompatible sustained-release material into said internal body cavity;

applying said biocompatible sustained-release material to at least part of the internal surface of said internal body cavity;

applying force to said material, thereby spreading it over at least part of the internal surface of said internal cavity;



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causing said biocompatible sustained-release material to adhere to said internal surface of said internal body cavity; and,

releasing said therapeutic agent into said internal body cavity under conditions chosen from the group consisting of:

- a temperature of 36-42° C.; pH in the range of 5.5-8.0, and at a rate of 80% in a time range of 3 to 30 hours;
- a temperature of 36-42° C.; pH in the range of 1-9.0, and at a rate of 80% in a time range of 3 to 30 hours; and,
- a temperature of 36-42° C.; pH in the range of 1-9.0, and at a rate of 80% in a time range of 2 to 4 weeks.

It is a further object of this invention to disclose such a method, additionally comprising a step of providing said material with at least one component selected from the group consisting of adhesive and thickening compounds; at least one substance selected from the group consisting of polycarbophil, cellulose, microcrystalline cellulose, cellulose derivatives, dicalcium phosphate, lactose, PVP and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides, fats and fatty acid derivatives and any combination thereof; pH-modifying substances; at least one substance selected from the group consisting of ethylcelluloses and polymethacrylates, cellulose acetate, cellulose acetate butyrate and any combination thereof; plasticizers; at least one substance selected from the group consisting of polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC), cellulose acetate, ethylcellulose and polymethacrylates, high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, poly(hydroxyalkyl methacrylate), alginates, galactomannans, and any combination thereof; at least one substance chosen from the group consisting of polyethylene glycols, PVP, PVA, HPC, hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans urea, salts, sodium chloride, potassium chloride, ammonium chloride, sugars, sucrose, lactose, glucose, fructose, maltose, sugar alcohols, mannitol, sorbitol, xylitol, lactitol, and any combination thereof; at least one substance chosen from the group consisting of hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, alkylcelluloses, hydroxy-alkylcelluloses hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch, starch derivatives and any combination thereof; and any combination thereof.

It is a further object of this invention to disclose such a method, wherein said step of releasing said therapeutic material into said internal body cavity further comprises a step of dissolving said biocompatible sustained-release material in body fluid found within said internal body cavity, whereby said therapeutic agent is released from said biocompatible sustained-release material.

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It is a further object of this invention to disclose such a method, wherein said step of applying force to said material further comprises a step of filling said catheter balloon with a liquid and positioning the patient to utilize the gravitational forces directly toward the target tissue during the solidification of the material and cause optimal adhesion to that target tissue.

It is a further object of this invention to disclose such a method, wherein said step of applying force to said material further comprises a step of changing the position of the patient before applying partial doses of material to enable substantially full coating of the whole targeted internal cavity surface.

It is a further object of this invention to disclose such a method, wherein said step of applying force to said material further comprises inserting a magnetic material chosen from the group consisting of a magnet, a magnetic metal, and a ferromagnetic liquid into said balloon; and applying an external magnetic field such that the interaction said magnetic material and said external magnetic field causes said magnetic material to move within said balloon, thereby applying force to at least part of the internal surface of said internal cavity.

It is therefore an object of the present invention to disclose a hydrophilic biocompatible sustained-release material comprising Pluronic F-127 and Hydroxypropylmethylcellulose (HPMC) in amounts effective to produce a hydrogel composition of sufficiently low viscosity at room temperature to be injectable into an internal body cavity via a tube inserted within a urinary catheter, trocar or the working channel of an endoscope.

It is a further object of this invention to disclose such a material, further comprising PEG-400 or PEG-800.

It is a further object of this invention to disclose such a material as defined in any of the above, additionally comprising at least one active ingredient (API).

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said API comprises excipients selected from acids or buffer substances adapted to modify the pH so as to reduce the dependence of said release of active ingredient on the pH of the release medium.

It is a further object of this invention to disclose such a material as defined in any of the above, additionally comprising at least one more compounds selected from adhesive and thickening compounds; bonding agents; pH-modifying substances; diffusion coating; plasticizers; matrix permeability increasing components; swellable excipients matrix-forming polymers; diffusion-controlled or pulsatile formulations; reverse thermal gelation agents or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said adhesive and thickening compounds are selected from a group consisting of polycarbophil, acrylic acid crosslinked, divinyl glycol, hydroxypropylmethylcellulose (HPMC), polyvinylpyrrolidone (PVP), methylcellulose (MC), hydroxy-propylcellulose (HPC), other hydroxyalkylcelluloses, hydroxyalkylmethylcelluloses, carboxy-methylcelluloses and salts thereof, polyacrylic acids, polymethacrylates, gelatin, starch or starch derivatives, as well as gums like guar gum and xanthan gum or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said bonding agents are selected from a group consisting of polycarbophil, cellulose, microcrystalline cellulose, cellulose derivatives such as, for example, HMPC, HPC and low-substituted hydroxypropylcellulose (L-HPC), dicalcium phosphate, lac-

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tose, PVP and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides (e.g. alginic acid, alginates, galactomannans) waxes, fats and fatty acid derivatives or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said pH-modifying substances are selected from a group consisting of acids, bases and buffer, adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, toluenesulphonic acid, trometamol, tartaric acid. Citric acid, succinic acid, tartaric acid, potassium hydrogen tartrate are preferably employed or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said diffusion coating are selected from a group consisting of ethylcelluloses and polymethacrylates such as, for example, EUDRAGIT® NE, EUDRAGIT® RS and RL, cellulose acetate and cellulose acetate butyrate or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said plasticizers are selected from a group consisting of citric acid derivatives, triethyl citrate, tributyl citrate, acetyl triethyl citrate, phthalic acid derivatives, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, benzoic acid and benzoic esters, other aromatic carboxylic esters, trimellithic esters, aliphatic dicarboxylic esters, dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters, glycerol monoacetate, glycerol diacetate or glycerol triacetate, polyols, glycerol, 1,2-propanediol, polyethylene glycol of varying chain length, fatty acids and derivatives, glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol, fatty acid alcohols, cetyl alcohol, cetylstearyl alcohol or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein the proportion of the plasticizer is from 0 to 50%, preferably 0 to 35% of the hydrogel composition.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said water-soluble polymers are selected from a group consisting of polymers polyethylene glycols, PVP, PVA, HPMC, HPC, hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans urea, salts, sodium chloride, potassium chloride, ammonium chloride, sugars, sucrose, lactose, glucose, fructose, maltose, sugar alcohols, mannitol, sorbitol, xylitol, lactitol, or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said swellable excipients are selected from a group consisting of polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC), cellulose acetate, ethylcellulose and polymethacrylates, high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose,

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crosslinked sodium carboxymethylstarch, poly(hydroxyalkyl methacrylate), alginates and galactomannans and mixtures thereof or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said reverse thermal gelaton compositions are selected from a group consisting of Poloxamers, Poloxamer 407 or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said water-swelling matrix-forming polymers compositions are selected from a group consisting of hydroxy-propylmethylcelluloses (HPMC), hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, alkylcelluloses, hydroxyalkylcelluloses hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans such as, for example, guar and carob flour, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch or starch derivatives or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is formulated as a homogeneous mixture.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is administered orally, topically, intranasal, vaginally, rectal, ocular and parenteral routes.

It is a further object of this invention to disclose such a material as defined in any of the above, further comprising lidocaine.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is soluble in at least one body fluid chosen from the group consisting of urine, serous fluids, and lymphatic fluids.

It is a further object of this invention to disclose such a material, wherein the solubility of said material is sufficiently high that said material will completely degrade in less than 4 weeks after incorporation into an internal body cavity.

It is a further object of this invention to disclose such a material, wherein the solubility of said material is sufficiently high that said material will completely degrade in less than 24 hours after incorporation into an internal body cavity.

It is a further object of this invention to disclose such a material, wherein the solubility of said material is sufficiently high that said material will completely degrade in less than 18 hours after incorporation into an internal body cavity.

It is a further object of this invention to disclose such a material, wherein the solubility of said material is sufficiently high that said material will completely degrade in less than 16 hours after incorporation into an internal body cavity.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is adapted to exhibit reverse thermal gelling properties.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is characterized by a viscosity of less than 200 Pa·s at a range of 8° C. to 25° C. and greater than 3000 Pa·s at a range of 35° C.-37° C.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is characterized by a viscosity of less than 200 Pa·s at 10° C. and greater than 3000 Pa·s at 37° C. It is a further object of this invention to disclose such a material, wherein said material is

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characterized by a viscosity of less than 200 Pa·s at 10° C. and greater than 3500 Pa·s at 37° C.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein the instillation temperature of said material is between 20° C. and 42° C.

It is a further object of this invention to disclose such a material, wherein said material is characterized by a gel point below 20° C.

It is a further object of this invention to disclose such a material as defined in any of the above, adapted to adhere to the surface of mucosal tissue.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is characterized by a "rolling ball" adhesiveness according to the ASTM D-3121-94 standard is less than 2 cm.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is characterized by a "peel strength" adhesiveness according to the ASTM D-2256-03 standard is at least 1N/cm<sup>2</sup>.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is characterized by a work of adhesion of at least 0.5 mJ.

It is a further object of this invention to disclose such a material, wherein said material is characterized by a work of adhesion of at least 0.7 mJ.

It is a further object of this invention to disclose such a material, wherein said material is characterized by a work of adhesion of at least 1 mJ.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is characterized by a peak detachment force of at least 1.3 N.

It is a further object of this invention to disclose such a material, wherein said material is characterized by a peak detachment force of at least 14.4 N.

It is a further object of this invention to disclose such a material, wherein said material is characterized by a peak detachment force of at least 6.3 N.

It is a further object of this invention to disclose such a material, wherein said mucosal tissue comprises interior wall of at least one selected from a group consisting of the urinary bladder, mouth, nasal and paranasal sinus, gallbladder, esophagus, rectum, lungs, vagina, uterus, stomach, renal pelvis, pleura, abdomen, peritoneum, pelvis, liver, kidney, heart, intestine, brain, vertebral column, or any combination thereof.

It is a further object of this invention to disclose such a material, adapted to remain adherent to said mucosal tissue during the natural expansion on contraction of said urinary bladder or other organs.

It is a further object of this invention to disclose such a material as defined in any of the above, further comprising an effective amount of a therapeutic agent.

It is a further object of this invention to disclose such a material, comprising 20-30% Pluronic F-127; 0-1.8% PEG-400; 0.1%-0.3% HPMC; an effective amount of a therapeutic agent; and the balance water.

It is a further object of this invention to disclose such a material, comprising 20-30% Pluronic F-127; 0-2.5% PEG-400; 0.05%-0.5% HPMC; an effective amount of a therapeutic agent; and the balance water.

It is a further object of this invention to disclose such a material, wherein said therapeutic agent is chosen from the group consisting of Mitomycin C, Doxorubicin (with or without antibiotics), Valrubicin, and Gemcitabine, Thiotepa, Ethoglucid (Epodyl), Epirubicin, Pirarubicin, Apaziquone and Vicinium.

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It is a further object of this invention to disclose such a material, wherein said therapeutic agent is mitomycin C.

It is a further object of this invention to disclose such a material, wherein said mitomycin C is present in a concentration of 0.05%-0.2%.

It is a further object of this invention to disclose such a material, wherein said mitomycin C is present in a concentration of 0.025%-0.3%.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein the solubility of said material is sufficiently low that said therapeutic agent is continuously released for at least 12 hours.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein the solubility of said material is sufficiently low that said therapeutic agent is continuously released for at least 2 hours.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein the solubility of said material is sufficiently low that said therapeutic agent is continuously released for at least 16 hours.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein the solubility of said material is sufficiently low that said therapeutic agent is continuously released for at least 18 hours.

It is a further object of this invention to disclose the use of the material as defined in any of the above in a sustained-release topical treatment of a condition affecting an internal body cavity.

It is a further object of this invention to disclose the use of the material as defined in any of the above in a sustained-release topical treatment for at least one selected from a group of internal cavities that includes, among others, the urinary bladder, mouth, nasal and paranasal sinus, gallbladder, esophagus, rectum, lungs, vagina, uterus, stomach, renal pelvis, pleura, abdomen, peritoneum, pelvis, liver, kidney, heart, intestine, brain, vertebral column, etc.

It is a further object of this invention to disclose such a material as defined in any of the above, additionally comprising at least one active ingredient (API).

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material comprises excipients selected from acids or buffer substances adapted to modify the pH so as to reduce the dependence of said release of active ingredient on the pH of the release medium.

It is a further object of this invention to disclose such a material as defined in any of the above, additionally comprising at least one more compounds selected from adhesive and thickening compounds; bonding agents; pH-modifying substances; diffusion coating; plasticizers; matrix permeability increasing components; swellable excipients matrix-forming polymers; diffusion-controlled or pulsatile formulations; reverse thermal gelation agents or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said adhesive and thickening compounds are selected from a group consisting of polycarboxylic, acrylic acid crosslinked, divinyl glycol, hydroxypropylmethylcellulose (HPMC), polyvinylpyrrolidone (PVP), methylcellulose (MC), hydroxy-propylcellulose (HPC), other hydroxyalkylcelluloses, hydroxyalkylmethylcelluloses, carboxy-methylcelluloses and salts thereof, polyacrylic acids, polymethacrylates, gelatin, starch or starch derivatives, as well as gums like guar gum and xanthan gum or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said bonding agents are selected from a group consisting of polycarboxylic,



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cellulose, microcrystalline cellulose, cellulose derivatives such as, for example, HPMC, HPC and low-substituted hydroxypropylcellulose (L-HPC), dicalcium phosphate, lactose, PVP and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides (e.g. alginic acid, alginates, galactomannans) waxes, fats and fatty acid derivatives or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said pH-modifying substances are selected from a group consisting of acids, bases and buffer, adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, toluenesulphonic acid, trometamol, tartaric acid. Citric acid, succinic acid, tartaric acid, potassium hydrogen tartrate are preferably employed or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said diffusion coating are selected from a group consisting of ethylcelluloses and polymethacrylates such as, for example, EUDRAGIT® NE, EUDRAGIT® RS and RL, cellulose acetate and cellulose acetate butyrate or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said plasticizers are selected from a group consisting of citric acid derivatives, triethyl citrate, tributyl citrate, acetyl triethyl citrate, phthalic acid derivatives, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, benzoic acid and benzoic esters, other aromatic carboxylic esters, trimellithic esters, aliphatic dicarboxylic esters, dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters, glycerol monoacetate, glycerol diacetate or glycerol triacetate, polyols, glycerol, 1,2-propanediol, polyethylene glycol of varying chain length, fatty acids and derivatives, glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol, fatty acid alcohols, cetyl alcohol, cetylstearyl alcohol or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein the proportion of the plasticizer is from 0 to 50%, preferably 0 to 35% of the hydrogel composition.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said water-soluble polymers are selected from a group consisting of polymers polyethylene glycols, PVP, PVA, HPMC, HPC, hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextran urea, salts, sodium chloride, potassium chloride, ammonium chloride, sugars, sucrose, lactose, glucose, fructose, maltose, sugar alcohols, mannitol, sorbitol, xylitol, lactitol, or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said swellable excipients are selected from a group consisting of polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC), cellulose acetate, ethylcellulose and polymethacrylates, high-molecu-

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lar weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, poly(hydroxyalkyl methacrylate), alginates and galactomannans and mixtures thereof or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said reverse thermal gelatin compositions are selected from a group consisting of Poloxamers, Poloxamer 407 or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said water-swelling matrix-forming polymers compositions are selected from a group consisting of hydroxy-propylmethylcelluloses (HPMC), hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, alkylcelluloses, hydroxyalkylcelluloses hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans such as, for example, guar and carob flour, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch or starch derivatives or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is administered orally, topically, intranasal, vaginally, rectal, ocular and parenteral routes.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said API is released at temperature of 36-42° C.; pH in the range of 5.5-8.0, at a rate of 80% in a time range of 3 to 30 hours.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said API is released at temperature of 36-42° C.; pH in the range of 1-8.0, at a rate of 80% in a time range of 2 hours to 4 weeks.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said API is dissolved, suspended and/or solid, amorphous or crystalline form.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said API is provided in various particle sizes, in unground, ground or in micronized form.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is administered topically; further wherein said API is selected from a group consisting of Antineoplastic drugs; Chemotherapeutic agents; Anti-infective agents, Antimicrobial drugs, Antiparasitic agents, Antivirals; Antihemorrhagics, Antithrombotic agents, antianemic drugs, Dermatologic drugs, antifungals, antiseptic, Genito-urinary system drugs, Gastrointestinal system, antiobesity, acid related disorders, Metabolism drugs, Anti-inflammatory product, Musculoskeletal system acting drugs; Respiratory drugs, Otolological drugs, Anti-infective drugs, Corticosteroids drugs, Analgesics drugs, GeneTherapy, Antiparasitics drugs, Growth factors, VEGF, Inhibitory factors, LIF or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material further comprising at least one selected from a group consisting of Poly (propylene oxide)—PPO, Poly (lactide-co-glycolic acid)—PLGA, Poly (N-isopropylacrylamide)—

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PNIPAM, Poly (propylene fumarate)—PPF, Poly (urethane)—PU, Poly (organophosphazene)—POP, Poloxamers of the type PEO-PPO-PEO (Poly (ethylene oxide), Poly (propylene oxide), Poly (ethylene oxide)) such as poloxamer 68, 88, 98, 108, 124, 127, 188, 237, 338 and 407, Stearic Acid, Poly (acrylic acid), Glyceryl Stearate, Cetearyl Alcohol, Sodium Stearoyl Lactylate, Hydroxy-Lenolin or any combination thereof.

It is a further object of this invention to disclose such a material, wherein said material is used as biological glue.

It is a further object of this invention to disclose a method for administering a therapeutic agent to the internal surface of an internal body cavity, comprising:

incorporating an effective amount of said therapeutic agent into a biocompatible sustained-release material;

inflating a balloon to open said internal body cavity to a substantially symmetrical shape;

introducing said biocompatible sustained-release material into said internal body cavity;

applying said biocompatible sustained-release material to at least part of the internal surface of said internal body cavity;

applying force to said material, thereby spreading it over at least part of the internal surface of said internal cavity;

causing said biocompatible sustained-release material to adhere to said internal surface of said internal body cavity; and,

releasing said therapeutic agent into said internal body cavity.

It is a further object of this invention to disclose such a method as defined in any of the above, additionally comprising step of providing said material with at least one active ingredient (API).

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said material comprises excipients selected from acids or buffer substances adapted to modify the pH so as to reduce the dependence of said release of active ingredient on the pH of the release medium.

It is a further object of this invention to disclose such a method as defined in any of the above, additionally comprising step of providing said material with at least one more compounds selected from adhesive and thickening compounds; bonding agents; pH-modifying substances; diffusion coating; plasticizers; matrix permeability increasing components; swellable excipients matrix-forming polymers; diffusion-controlled or pulsatile formulations; reverse thermal gelation agents or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said adhesive and thickening compounds are selected from a group consisting of polycarboxylic acid crosslinked, divinyl glycol, hydroxypropylmethylcellulose (HPMC), polyvinylpyrrolidone (PVP), methylcellulose (MC), hydroxy-propylcellulose (HPC), other hydroxyalkylcelluloses, hydroxyalkylmethylcelluloses, carboxy-methylcelluloses and salts thereof, polyacrylic acids, polymethacrylates, gelatin, starch or starch derivatives, as well as gums like guar gum and xanthan gum or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said bonding agents are selected from a group consisting of polycarboxylic acid, cellulose, microcrystalline cellulose, cellulose derivatives such as, for example, HMPMC, HPC and low-substituted hydroxypropylcellulose (L-HPC), dicalcium phosphate, lactose, PVP and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol,

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polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides (e.g. alginic acid, alginates, galactomannans) waxes, fats and fatty acid derivatives or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said pH-modifying substances are selected from a group consisting of acids, bases and buffer, adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, toluenesulphonic acid, trometamol, tartaric acid. Citric acid, succinic acid, tartaric acid, potassium hydrogen tartrate are preferably employed or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said diffusion coating are selected from a group consisting of ethylcelluloses and polymethacrylates such as, for example, EUDRAGIT® NE, EUDRAGIT® RS and RL, cellulose acetate and cellulose acetate butyrate or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said plasticizers are selected from a group consisting of citric acid derivatives, triethyl citrate, tributyl citrate, acetyl triethyl citrate, phthalic acid derivatives, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, benzoic acid and benzoic esters, other aromatic carboxylic esters, trimellithic esters, aliphatic dicarboxylic esters, dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters, glycerol monoacetate, glycerol diacetate or glycerol triacetate, polyols, glycerol, 1,2-propanediol, polyethylene glycol of varying chain length, fatty acids and derivatives, glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol, fatty acid alcohols, cetyl alcohol, cetylstearyl alcohol or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein the proportion of the plasticizer is from 0 to 50%, preferably 0 to 35% of the hydrogel composition.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said water-soluble polymers are selected from a group consisting of polymerspolyethylene glycols, PVP, PVA, HPMC, HPC, hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans urea, salts, sodium chloride, potassium chloride, ammonium chloride, sugars, sucrose, lactose, glucose, fructose, maltose, sugar alcohols, mannitol, sorbitol, xylitol, lactitol, or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said swellable excipients are selected from a group consisting of polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC), cellulose acetate, ethylcellulose and polymethacrylates, high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl-

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starch, poly(hydroxyalkyl methacrylate), alginates and galactomannans and mixtures thereof or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said reverse thermal gelatin compositions are selected from a group consisting of Poloxamers, in particular Poloxamer 407 or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said water-swelling matrix-forming polymers compositions are selected from a group consisting of hydroxy-propylmethylcelluloses (HPMC), hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, alkylcelluloses, hydroxy-alkylcelluloses hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans such as, for example, guar and carob flour, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch or starch derivatives or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, additionally comprising step of administering said material orally, topically, intranasal, vaginally, rectal, ocular and parenteral routes or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said API is released at temperature of 36-42° C.; pH in the range of 5.5-8.0, at a rate of 80% in a time range of 3 to 30 hours.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said API is released at temperature of 36-42° C.; pH in the range of 1-8.0, at a rate of 80% in a time range of 2 to 4 weeks.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said API is released at temperature of 36-42° C.; pH in the range of 1-9.0, at a rate of 80% in a time range of 3 to 30 hours.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said API is dissolved, suspended and/or solid, amorphous or crystalline form.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said API is provided in various particle sizes, in unground, ground or in micronized form.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said material is administered topically; further wherein said API is selected from a group consisting of Antineoplastic drugs; Chemotherapeutic agents; Anti-infective agents, Antimicrobial drugs, Antiparasitic agents, Antivirals; Drugs acting on the blood and blood forming organs, Antihemorrhagics, Antithrombotic agents, antianemic drugs, Dermatologic drugs, antifungals, antiseptic, Genito-urinary system drugs, Gastrointestinal system, antiobesity, acid related disorders, Metabolism drugs, Anti-inflammatory product, Musculoskeletal system acting drugs; Neurological drugs, Respiratory drugs, Cardio-vascular drugs, Otolological drugs, Anti-infective drugs, Corticosteroids drugs, Analgesics and anesthetics drugs, GeneTherapy, Antiparasitics drugs, Growth factors, VEGF, Inhibitory factors, LIF or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, additionally compris-

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ing step of providing said material with at least one selected from a group consisting of Poly (propylene oxide)—PPO, Poly (lactide-co-glycolic acid)—PLGA, Poly (N-isopropylacrylamide)—PNIPAM, Poly (propylene fumerate)—PPF, Poly (urethane)—PU, Poly (organophosphazene)—POP, Poloxamers of the type PEO-PPO-PEO (Poly (ethylene oxide), Poly (propylene oxide), Poly (ethylene oxide)) such as poloxamer 68, 88, 98, 108, 124, 127, 188, 237, 338 and 407, Stearic Acid, Poly (acrylic acid), Glyceryl Stearate, Cetearyl Alcohol, Sodium Stearoyl Lactylate, Hydroxy-Lenolin or any combination thereof.

It is a further object of this invention to disclose such a method, wherein said biocompatible sustained-release material is the biocompatible sustained-release material as defined in any of the above.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said internal body cavity is at least one selected from a group of internal cavities that includes, among others, the urinary bladder, mouth, nasal and paranasal sinus, gallbladder, esophagus, rectum, lungs, vagina, uterus, stomach, renal pelvis, pleura, abdomen, peritoneum, pelvis, liver, kidney, heart, intestine, brain, vertebral column, etc.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said therapeutic agent is a therapeutic agent for treatment of superficial bladder cancer.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of introducing said biocompatible sustained-release material into said internal body cavity further comprises a step of introducing said biocompatible sustained-release material into said internal body cavity via a catheter.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of releasing said therapeutic material into said internal body cavity further comprises a step of dissolving said biocompatible sustained-release material in body fluid within said internal body cavity, whereby said therapeutic agent is released from said biocompatible sustained-release material.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying force to said material further comprises a step of filling said catheter balloon with water and positioning the patient to utilize the gravitational forces directly toward the target tissue during the solidification of the material and cause optimal adhesion to that target tissue.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying gravitational force to said material further comprises a step of changing the position of the patient before applying partial doses of material to enable substantially full coating of the whole targeted internal cavity surface.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying force to said material further comprises a step of filling said balloon with a liquid denser than water.

It is a further object of this invention to disclose such a method, wherein said liquid denser than water comprises a solution of salt in water, said solution having a density greater than 1.0 g/cm<sup>3</sup>.

It is a further object of this invention to disclose such a method, wherein said liquid denser than water comprises a solution of glucose in water, said solution having a density greater than 1.0 g/cm<sup>3</sup>.



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It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying force to said material further comprises steps of inserting a first magnetic means into said balloon; and, applying a second magnetic means such that the magnetic attraction of said first magnetic means and said second magnetic means causes said first magnet to move within said balloon, whereby said attraction applies force to at least part of the internal surface of said internal cavity.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying force to said material further comprises steps of introducing a ferromagnetic liquid into said balloon; and, applying magnetic means such that the magnetic attraction of said magnetic means and ferromagnetic particles suspended within said ferromagnetic liquid causes said ferromagnetic particles to move within said balloon, thereby applying force to at least part of the internal surface of said internal cavity.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying force to said material further comprises steps of introducing into said balloon a substance chosen from (a) a constant or electric magnet, (b) a piece of ferromagnetic material, and (c) a ferromagnetic liquid; placing the patient within an MRI apparatus; and, activating said MRI apparatus such that the magnetic field of said MRI apparatus causes said substance to move within said balloon, thereby applying force to at least part of said internal cavity.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein the solubility of said material is sufficiently high that said material will completely degrade in less than 4 weeks after incorporation into an internal body cavity.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said material is characterized by a viscosity of less than 200 Pa·s at a range of 10° C. to 25° C. and greater than 3000 Pa·s at a range of 35° C.-37° C.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said material is characterized by a viscosity of less than 200 Pa·s at 10° C. and greater than 3000 Pa·s at 37° C.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein the instillation temperature of said material is between 4° C. and 60° C.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said material comprising 20-30% Pluronic F-127; 0-1.8% PEG-400; 0.1%-0.3% HPMC; an effective amount of a therapeutic agent; and the balance water.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said material comprising 20-30% Pluronic F-127; 0-2.5% PEG-400; 0.05%-0.5% HPMC; an effective amount of a therapeutic agent; and the balance water.

It is a further object of this invention to disclose such a method as defined in any of the above, additionally comprising step of providing said material as biological glue.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein the weight of the balloon filled with a liquid denser than water is used for the application of the gel (utilizing its gravity).

#### BRIEF DESCRIPTION OF THE FIGURES

The invention disclosed herein is described with reference to the figures, in which:

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FIG. 1 presents a flow diagram of the creation of a hydrogel composition in a drug delivery system for treatment of internal cavities;

FIG. 2 presents schematic illustrations of micellar phases, formed by the polymer herein disclosed with increasing temperature;

FIG. 3 presents graphs illustrating the MMC cytotoxicity when different MMC concentrations are used in saline and in DTC-2 respectively;

FIG. 4 presents graphically the results of a study of the effect of botulinum toxin gel on contraction of animal bladder as model for overactive bladder contraction;

FIG. 5 presents graphs representing results of measurements of rheological parameters of the material according to several embodiments of the invention herein disclosed;

FIG. 6 presents a graph showing the delivery of MMC to pig bladder tissue by use of a gel according to one embodiment of the present invention;

FIG. 7 presents results of measurements of in vitro release of Lidocaine hydrochloride (10 and 20 mg/ml) from reverse thermal hydrogel (including 27% Ethylene Oxide/Propylene Oxide Block Copolymer, 1% PEG-400, 0.2% Hydroxypropylmethyl cellulose in water) and Cephalexin (1 mg/ml) from reverse thermal hydrogel (20.0% Pluronic F-127, 10% Pluronic F-68 (10.0%) 1.0% PEG-400 0.4% CMC sodium in water; and,

FIG. 8 shows results for the dissolution rate of hydrogels according to several different embodiments of the invention.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the following description, various aspects of the invention will be described. For the purposes of explanation, specific details are set forth in order to provide a thorough understanding of the invention. It will be apparent to one skilled in the art that there are other embodiments of the invention that differ in details without affecting the essential nature thereof. Therefore the invention is not limited by that which is illustrated in the figure and described in the specification, but only as indicated in the accompanying claims, with the proper scope determined only by the broadest interpretation of said claims.

As used herein, the term “internal cavity” is used to describe parts in the body that are either accessible through an orifice—e.g., mouth, bladder, intestine, esophagus, rectum, lungs, vagina, stomach, renal pelvis, etc.—or by way of minimally invasive, surgery—e.g., pleura, abdomen, peritoneum, pelvis, etc. The definition includes artificially made or enlarged cavities in adipose tissues and fibrous capsules in internal organs such as the kidney, heart, intestine, etc. that are accessible by image guided laparoscopic techniques.

As used herein, the term “DTC” is used to refer generically to the materials disclosed in the present invention. The terms “DTCx” and “DTC-n” (where n is an integer) are used to refer to particular embodiments, either generically (DTCx) or specifically (e.g. DTC-2).

The present invention provides a bioerodible, biocompatible gel mixed with an active agent, such as chemotherapy agent like MMC or gemcitabine, or immunotherapy such as BCG (bacillus Calmette-Guérin), which is inserted into the upper urinary tract via a designated catheter, solidifies and forms a drug reservoir at the destined treatment area such as the renal pelvis. The diffusion of the drug from the gel and the erosion of the gel by the urine or the biodegradability of the gel, deliver drug to the tissue-producing prolonged high topical drug concentration but low systemic exposure. This, the

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system increases bioavailability, reduces toxicity and improves treatment efficacy. Furthermore, loading the material with significant concentration of chemotherapy agent and applying the material directly over a tumor for a prolonged duration, may ablate non-resected tumors that are in close contact with the material.

The present invention provides a design of such gel compositions that is based on the characteristics of the internal cavities to be treated and the specific requirements for said treatments in order to determine the required properties of hydrogel systems that can satisfy all these requirements. A flow diagram for creation of hydrogel composition is illustrated in FIG. 1. This structured set of gel properties enables the formulation of gel systems for optimal drug delivery. The present invention provides a structured design and test flow that assures optimal hydrogels for optimal treatments.

In some embodiments, the present invention additionally provides a bioerodible, biocompatible hydrogel that is mixed with a neurological drug such as botulinum toxin, is inserted into the bladder, solidifies and forms a drug reservoir inside the bladder. The erosion of the material in the urine, promotes topical drug delivery and increases the drug affinity to the bladder wall tissue producing high topical drug concentration in the bladder wall and at the same time keeps a low systemic exposure. The system provides drug delivery to the entire bladder resulting in total tissue contact with the delivered neurological drug as opposed to delivery induced by local injections.

The invented material includes a mixture of hydrogel with botulinum toxin (A, B, Cl, D, E, F and G and equivalent neurological drugs) for the treatment of disorders characterized by bladder spasms (eg. urge incontinence due to unstable bladder or unstable detrusor, sphincter or neurogenic bladder, etc.). The hydrogel mixed with botulinum toxin will be instilled into the bladder without injections into the bladder tissue and its effect will be.

The present invention also includes the use of the novel pharmaceutical formulation or admix for producing medications which are intended for the treatment and/or prevention of disorders in humans. These systems contain drugs embedded in a slowly degrading biocompatible admix and are combined with administering means, so that the materials can be introduced in a minimally invasive manner into a body cavity and provide a prolonged exposure of the cavity tissue to the drug, thus improving the treatment efficacy in terms of improved therapeutic effect of the drug and reduced tissue damage. The admix/mixture is biocompatible and dissolves in body fluids such as urine, serous fluids or lymphatic fluids, and then it is expelled from the body.

The aim of the prolonged exposure of target tissue to drugs released from the coating is to enhance the efficacy of the drug in topical treatment of that target tissue, while reducing potential systemic adverse effects to other organs. As a specific example, the aim of the prolonged exposure of cancer cells to an anticancer drug released from the coating is to enhance the efficacy of the drug in killing cancer cells and, therefore, potentially reduce the recurrence rate of cancer tumors, while reducing the systemic effect of chemotherapy on other parts of the patient body.

The homogeneous coating obtained in the invention disclosed herein, i.e., a solidified, unified and homogeneous layer that provides continuous sustained release of therapeutic agents upon the inner surface of an internal body cavity, as herein disclosed, has to the inventors' knowledge never been produced or used clinically.

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Thus, it is one object of the present invention to provide a material that includes active pharmaceutical ingredients (APIs) as a part of its basic formulation.

The current invention provides a platform for the redesign of drugs to make them suitable for topical administration. Company studies demonstrated solubility and first order sustained release of Mytomicin C, Doxorubicin and Gemcitabin (groups 1 & 2), Abamectin (group 3), exogenous glycosaminoglycan, group 4), Naproxen (group 5), lidocaine and voltaren (group 6).

Among the drugs that can be administered topically are drugs that belong to the following families:

1. Antineoplastic drugs
  2. Chemotherapeutic agents
  3. Anti-infective agents (e.g. Antimicrobial drugs, Antiparasitic agents, Antivirals)
  4. Genito-urinary system drugs
  5. Anti-inflammatory products
  6. Analgesics
  7. Musculoskeletal system acting drugs
  8. Drugs acting on the blood and blood forming organs (Antihemorrhagics, Antithrombotic agents, antianemic drugs)
  9. Dermatologic drugs (antifungals, antiseptic)
  10. Gastrointestinal system (antiobesity, acid related disorders)
  11. Metabolism drugs
  12. Neurological drugs
  13. Respiratory drugs including nasal drugs
  14. Cardio-vascular drugs
  15. Otolological drugs
  16. Anti-infective drugs
  17. Corticosteroids drugs
  18. Analgesics drugs
  19. Antiparasitics drugs
  20. Anasthetic Drugs
- In other cases, the topical treatment is just evolving:
21. Growth factor (e.g., for treatment of heart muscle ischemia)
  22. Gene Therapy agents
  23. Mucin
  24. Hyaluronic Acid

Drugs can be embedded as part of the invented materials as a single therapeutic agent or as a combination. As an example, a mixture containing exogenous glycosaminoglycan and Naproxen can be combined in a specific material for the treatment of interstitial cystitis for alleviating the inflammation symptoms and replacing the damaged mucosal lining of the urinary bladder cavity that is typical for this disease.

The present invention provides a formulation/mixture which release active ingredients (API) in a controlled fashion over a prolonged period. It is further an object of the present invention to provide medicament formulations with particular release profiles through which the prior art problems. As an example an average release rate between 80% in 6 hours and 80% in 24 hours is maintained.

As standard, chemotherapy drugs are administered at a maximal concentration level that is tolerable by patients. The present invention study results demonstrate that a further improvement in efficacy can be gained by increasing the exposure time to chemotherapy drugs. This is at the core of the present invention.

In addition, the use of such formulation allows reduction of the frequency of administration thus leads to improved patient's compliance.

A longer exposure time of the API has distinct advantages and it is expected that a prolonged exposure with an API on



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use of a medicament with controlled release of active ingredient makes it possible to prolong substantially the time window in which improved therapy can be achieved. The use of the novel medicinal forms with controlled release of active ingredient is expected to achieve substantially more constant drug levels and avoid the occurrence of level peaks, thus improving for example the therapeutic efficacy and reducing the frequency and intensity of unwanted side effects.

In addition, the use of such admix/formulation/mixture allows the frequency of administration to be reduced and thus leads to improved acceptance and compliance by the patient.

It is expected as well that controlled-release of APIs prolong exposure without the occurrence of an increase in side effects, an adverse effect on reliability and safety of therapies. According to a preferred embodiment of the present invention the admix/formulation/mixture described above, is for example in the form of active ingredient-containing hydrogels. These diffusion-controlled systems may be completely diluted in the hydrogel admix/formulation/mixture or can be multiparticulate, i.e. they may consist of a large number of coated cores such as, for example, of microencapsulated APIs, where appropriate together with conventional excipients and carriers, as defined below for example, is applied and subsequently coated with a diffusion coating which may comprise plasticizers and other excipients. The diffusion-controlled systems according to the invention may additionally consist of homogeneous active ingredient-containing cores which are produced for example by granulation, rotor granulation, fluidized bed agglomeration, tableting, wet extrusion or melt extrusion, where appropriate with spheronization, and are coated with a diffusion coating which may comprise plasticizers and other excipients.

According to one embodiment, the present invention may provide a combination of APIs, one or more diluted or suspended in the gel and one or more microencapsulated for slower release effect. For example, an anesthetic like lidocaine dissolved in the admix/formulation/mixture for immediate anesthetic effect and encapsulated MMC for cancer treatment that is released after the bladder wall is insensitive and the patient can stand the MMC therapy.

In a preferred embodiment of this invention, the active ingredient-containing particles comprise excipients such as, for example, acids or buffer substances which modify the pH and thus contribute to reducing the dependence of the release of active ingredient on the pH of the release medium.

According to a preferred embodiment of the present invention the material/formulation/mixture described above, additionally comprises at least one ingredient selected from:

- (a) adhesive and thickening compounds;
- (b) bonding agents;
- (c) pH-modifying substances;
- (d) diffusion coating;
- (e) plasticizers;
- (f) Tight junction modifiers & permeability enhancers;
- (g) matrix permeability increasing components;
- (h) swellable excipients matrix-forming polymers;
- (i) diffusion-controlled or pulsatile formulations; and,
- (j) reverse thermal gelation agents.

The adhesive and thickening compounds preferably used in the production of coated neutral pellets (e.g. consisting of sucrose, microcrystalline cellulose, citric acid) are polycarboxophil (polymer of acrylic acid crosslinked with divinyl glycol), hydroxypropylmethylcellulose (HPMC) and polyvinylpyrrolidone (PVP). It is likewise possible to employ other naturally, synthetic or partially synthetic polymers such as, for example methylcellulose (MC), hydroxy-propylcellulose (HPC), other hydroxyalkylcelluloses and hydroxyalkylmeth-

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ylcelluloses, carboxy-methylcelluloses and salts thereof, polyacrylic acids, polymethacrylates, gelatin, starch or starch derivatives, as well as gums like guar gum and xanthan gum.

The bonding agents employed for the production of active ingredient-containing microcapsules are for example polycarboxophil, cellulose, microcrystalline cellulose, cellulose derivatives such as, for example, HMPCC, HPC and low-substituted hydroxypropylcellulose (L-HPC), dicalcium phosphate, lactose, PVP and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides (e.g. alginic acid, alginates, galactomannans) waxes, fats and fatty acid derivatives. The pH-modifying substances such as, for example, acids, bases and buffer substances are incorporated into the active ingredient-containing core. Addition of these substances makes it possible to reduce markedly the pH-dependence of the release of the APIs. Examples of suitable excipients which modify the pH in the active ingredient-containing cores are: adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, toluenesulphonic acid, trometamol, tartaric acid. Citric acid, succinic acid, tartaric acid, potassium hydrogen tartrate are preferably employed. Particularly suitable for producing the diffusion coating are ethylcelluloses and polymethacrylates such as, for example, EUDRAGIT® NE, EUDRAGIT® RS and RL. However, other materials such as, for example, cellulose acetate and cellulose acetate butyrate can also be employed as film-forming diffusion-controlling polymers. Examples of plasticizers used are citric acid derivatives (e.g. triethyl citrate, tributyl citrate, acetyl triethyl citrate), phthalic acid derivatives (e.g. dimethyl phthalate, diethyl phthalate, dibutyl phthalate), benzoic acid and benzoic esters, other aromatic carboxylic esters (e.g. trimellithic esters), aliphatic dicarboxylic esters (e.g. dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters), glycerol monoacetate, glycerol diacetate or glycerol triacetate, polyols (e.g. glycerol, 1,2-propanediol, polyethylene glycol of varying chain length), fatty acids and derivatives (e.g. glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol) and fatty acid alcohols (e.g. cetyl alcohol, cetylstearyl alcohol).

The nature and amount of the plasticizer are chosen so that the above-defined release according to the invention and the necessary stability of the medicinal forms is achieved. The proportion of the plasticizer is from 0 to 50%, preferably 0 to 35%, particularly preferably 0 to 25% based on the mass of the hydrogel composition.

The release rate according to the invention is controlled by the gel composition. Certain components may increase the permeability of the admix/formulation/mixture including water-soluble polymers such as, for example, polyethylene glycols, PVP, PVA, HPMC, HPC, hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans or other soluble substances such as, for example, urea, salts (sodium chloride, potassium chloride, ammonium chloride, etc.), sugars (sucrose, lactose, glucose, fructose, maltose etc.) and sugar alcohols (mannitol, sorbitol, xylitol, lactitol, etc.). Based on the mass of the hydrogel, the amount of the water-soluble poly-

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mers ranges from 0 to 50%, preferably 0 to 35%, particularly preferably 0 to 20%, increasing permeability components may be employed.

A further aspect of the present invention are coated admix/formulation/mixture which comprise one or more swellable excipients which, on penetration of liquid through the membrane, swell greatly and, through the swelling and volume expansion, cause the coating to split. The splitting of the coating makes it possible for the medicinal substance to be released from the admix/formulation/mixture, usually in pulsatile form. Swellable excipients which these formulations may comprise are, for example, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC). Examples of suitable coating materials are cellulose acetate, ethylcellulose and polymethacrylates.

The described diffusion-controlled or pulsatile formulations can be employed directly and unmodified as medicinal form. However, they may also be further processed, where appropriate with addition of excipients, to the final admix/formulation/mixture. In order to achieve a desired release profile it is also possible to combine different coated formulations in one medicinal form, and administration of an initial dose can take place for example by combination with rapid-release formulation particles, e.g. uncoated pellets, granules or powder.

In a further embodiment of the admix/formulation/mixture containing the controlled release ingredient. These so-called admix/formulation/mixture release the active ingredient by diffusion and/or erosion.

The mass ratio of active ingredient to the total mass of the admix/formulation/mixture in these novel formulations is in the range from 1:1 to 1:10,000, preferably in the range from 1:2 to 1:1,000.

admix/formulation/mixture which can be employed are water-soluble, water-swellable or water-insoluble substances. The novel formulations preferably comprise one or more water-swellable polymers.

Preference is additionally given to medicinal preparations in the context of this invention which comprise water-soluble, hydrogel-forming polymers, these polymers having a nominal viscosity of at least 0.015 Pa s, preferably at least 0.050 Pa s (measured as 2% strength aqueous solution at 20° C.).

A preferred family of candidates to be utilized as a basis for obtaining said hydrogel is group of tri-block copolymers designated as PEG-PPG-PEG (PEG=Polyethylene glycol and PPG=Polypropylene glycol) and called Poloxamers, that produce reverse thermal gelation compositions, i.e., with the characteristic that their viscosity increases with increasing temperature up to a point from which viscosity again decreases. In particular, Poloxamer 407 possesses a gelling temperature which is above 10° C. but below the human body temperature, i.e., 37° C. This characteristic may confer the ability of a composition containing the compound to be injected or infused in liquid state into a bodily inner cavity at a low temperature and, afterwards, as the composition warms, it solidifies into a gel, thus stabilizing upon the wall of the inner body cavity.

This characteristic has allowed Poloxamer 407 (PF-127) to be used as a carrier for most routes of administration including oral, topical, intranasal, vaginal, rectal, ocular and parenteral routes.

Poloxamer 407 (PF-127) is a nonionic surfactant composed of polyoxyethylene-polyoxypropylene triblock copolymers in a concentration ranging from 20-30%. At low

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concentrations ( $10^{-4}$ - $10^{-5}\%$ ) they form monomolecular micelles, but higher concentrations result in multimolecular aggregates consisting of a hydrophobic central core with their hydrophilic polyoxyethylene chains facing the external medium. Micellization occurs in dilute solutions of block copolymers in selected solvents above the critical micellar concentration, at a given temperature. At higher concentrations, above a critical gel concentration, the micelles can order into a lattice.

Aqueous solutions of poloxamers are stable in the presence of acids, alkalis, and metal ions. Commonly used poloxamers include the 88 (F-68 grade), 237 (F-87 grade), 338 (F-108 grade) and 407 (F-127 grade) types, which are freely soluble in water. The "F" designation refers to the flake form of the product. PF-127 has a good solubilizing capacity, low toxicity and is, therefore, considered a good medium for drug delivery systems.

PF-127 is a commercially available polyoxyethylene-polyoxypropylene triblock copolymer that possesses a general formula E106 P70 E106, with an average molar mass of 13,000. It contains approximately 70% ethylene oxide, which accounts for its hydrophilicity. It is one of the series of poloxamer ABA block copolymers. As said above, PF-127 aqueous solutions of 20 to 30% w/w have the interesting characteristic of reverse thermal gelation, i.e., they are liquid at refrigerated temperatures (4-5° C.), but gel upon warming to room temperature. The gelation is reversible upon cooling. This phenomenon, therefore, suggests that when poured onto the skin or injected into a body cavity, the gel preparation will form a solid artificial barrier and a sustained release depot. Furthermore, PF-127 has been reported to be the least toxic of commercially available copolymers.

Water-soluble or water-swellable matrix-forming polymers preferably employed are hydroxy-propylmethylcelluloses (HPMC), hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, other alkylcelluloses, hydroxy-alkylcelluloses and hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans such as, for example, guar and carob flour, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch or starch derivatives and mixtures of these substances.

In this connection, the admix/formulation/mixture according to the invention should preferably comprise at least 0.1-2.0% of a hydroxypropylmethylcellulose type whose nominal viscosity (measured as 2% strength aqueous solution at 20° C.) is at least 0.015 Pa s, preferably at least 0.050 Pa s. HPMC types preferably used have a degree of substitution of methoxy groups of 16.5-30%, particularly preferably 19-30%, and a degree of substitution of hydroxypropoxy groups of 4-32%, particularly preferably 4-12%.

In a particularly preferred embodiment of this invention, substances which control the pH in the admix/formulation/mixture are incorporated into the admix/formulation/mixture. The addition of such pH-modifying excipients and/or the addition of substances which dissolve or are dissolved out of the admix/formulation/mixture as the pH increases, and thus increase the porosity or permeability of the admix/formulation/mixture and/or promote erosion of the admix/formulation/mixture, makes it possible to achieve a virtually pH-independent release for these preferred embodiments of the present invention.

Examples of suitable excipients which can be added to the admix/formulation/mixture according to the invention to

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achieve release which is as far as possible pH-independent are the following substances: adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, cellulose phthalates, in particular cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate, cellulose succinates, in particular cellulose acetate succinate and HPMCAS, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, polymethacrylates (e.g. EUDRAGIT® types), toluenesulphonic acid, trometamol, tartaric acid. Citric acid, succinic acid, tartaric acid, HPMCAS, and polymethacrylates (e.g. EUDRAGIT® L) are preferably employed. If these excipients are present in the admix/formulation/mixture according to the invention, they are typically added in a proportion of from 10 to 50% based on the total mass of the admix/formulation/mixture.

Examples of plasticizing excipients in the hydrogel formulation are propylene glycol, glycerol, triethylene glycol, butanediols, pentanols, such as pentaerythritol, hexanols, long-chain alcohols, polyethylene glycols, polypropylene glycols, polyethylene/propylene glycols, silicones, phthalic acid derivatives (e.g. dimethyl phthalate, diethyl phthalate, dibutyl phthalate), benzoic acid and benzoic esters, other aromatic carboxylic esters (e.g. trimellithic esters), citric acid derivatives (e.g. triethyl citrate, tributyl citrate, acetyl triethyl citrate), aliphatic dicarboxylic esters (e.g. dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters), glycerol monoacetate, glycerol diacetate or glycerol triacetate, fatty acids and derivatives (e.g. glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol), fatty acid alcohols (e.g. cetyl alcohol, cetylstearyl alcohol), sugars, sugar alcohols and sugar derivatives (e.g. erythritol, isomalt, lactitol, mannitol, maltitol, maltodextrin, xylitol). The concentration of plasticizers is normally from 0 to 30%, preferably from 0 to 20% based on the total mass of the gel.

Examples of further suitable water-swallowable polymers which may be incorporated in the hydrogel are high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crosspovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, low-substituted hydroxypropylmethylcellulose (L-HPC), poly(hydroxyalkyl methacrylate), alginates and galactomannans and mixtures thereof.

The present invention further relates to the combination of formulations with different release properties, e.g. rapid-release and slow-release, in one medicinal form.

As described above, according to one embodiment of the present invention a admix/formulation/mixture which release active ingredients (API) in a controlled fashion over a prolonged period is provided.

If necessary, the pH can be adjusted to 1-8.0 with a buffer composition. The release is carried out at a temperature of 36-42° C.

If necessary, the pH can be adjusted to 1-5.5 with a buffer composition. The release is carried out at a temperature of 36-42° C.

If necessary, the pH can be adjusted to 5.5-9.0 with a buffer composition. The release is carried out at a temperature of 36-42° C.

The amount of active ingredient determined in this way is converted into percent by mass of the amount of active ingredient employed.

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The average release rate in the context of the present invention is defined via the time until the release of active ingredient reaches 80%, whereas the initial release describes the percentage release of active ingredient after 30 minutes.

The admix/formulation/mixture according to the invention with controlled release of active ingredient preferably have an average release rate of 80% in the time interval between 3 and 20 hours (80% in 3 hours and 80% in 20 hours).

The admix/formulation/mixture according to the invention with controlled release of active ingredient preferably have an average release rate of 80% in the time interval between 2 and 4 weeks (80% in 2 hours and 80% in 4 weeks).

In a particularly preferred embodiment of the medicament formulations with controlled release of active ingredient of the present invention, the formulation has an average release rate of 80% in the period from 3 and 18 hours and an initial release not exceeding 65% of the active ingredient in the first 30 minutes of release.

The admix/formulation/mixture according to the present invention can be formulated so that a relative low initial release of 0 to 30% in the first 30 minutes or a relative high initial release of 30 to 60% of the medicinal substance in the first 30 minutes of medicinal substance release is achieved.

In a preferred embodiment of the admix/formulation/mixture of the present invention is characterized by an average release rate of 80% in the period from 4 to 18 hours, this has a relatively low initial release of 0 to 25% in the first 30 minutes of release.

Another preferred configuration of the medicament formulations with controlled release of active ingredient has an average release rate of 80% in the period from 3 to 16 hours and is distinguished by a relatively high initial release of 35 to 60% in the first 30 minutes of release of active ingredient.

It should be emphasized that the admix/formulation/mixture with controlled release of active ingredient of this invention refers to all formulations in which the release of active ingredient is modified so that it takes place with a slower delivery rate than from rapid-release medicinal forms such as, for example, a conventional instillation procedure in the case of bladder cancer treatment.

Furthermore, the admix/formulation/mixture with controlled release of active ingredient of the present invention also include formulations with delayed release in which the delivery of the active ingredient is modified so that the release starts at a later time than with a conventional rapid-release medicinal form. The subsequent release from a delayed-release medicinal form may also take place in controlled fashion with a reduced release rate.

The admix/formulation/mixture according to the invention with controlled release of active ingredient also include formulations with pulsatile release, where the delivery of active ingredient takes place intermittently, and formulations in which different principles of controlled delivery of active ingredient are combined.

The admix/formulation/mixture of this invention additionally include also medicament formulations which comprise part of the active ingredient in rapid-release form and a further part of the active ingredient in controlled-release form.

The medicament formulations according to the invention may comprise the active ingredient is dissolved in, suspended and/or solid, amorphous or crystalline form. The active ingredient can be employed in various particle sizes, e.g. in unground, ground or in micronized form, to produce the admix/formulation/mixture according to the invention with controlled release of active ingredient.

According to one embodiment of the present invention provides a hydrogel composition that is intended to be used as



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a topical therapeutic agent, applied topically. Thus, it would be useful to have a device that allows the application of such said hydrogel composition once accessing a body organ (inner cavity) through an orifice (either natural or artificial), so as to allow the coating of the inner wall of the organ with said hydrogel gel. Such hydrogel composition will adhere well to said wall and will (i) allow the controlled release of the drug or drugs; (b) will enable the gradual dilution of the hydrogel; and, (c) expelled from the body in a reasonable period of time (e.g., 24 hrs).

According to another embodiment, cell line studies (see below) performed by the inventors of the present invention, demonstrate up to  $\times 30$  higher cell kill when cell lines are exposed to MMC for  $\times 10$  longer time or to  $\times 10$  higher concentrations.

As standard, chemotherapy drugs are administered at a concentration level that is tolerable by patients. The present invention study results demonstrate that a further improvement in efficacy can be gained by increasing the exposure time to chemotherapy drugs. This is at the core of the present invention's concept.

Several of the present invention's materials incorporate a variety of chemotherapy drugs for the treatment of bladder cancer—as non-limited examples, Mitomycin C, Doxorubicin, Valrubicin and Gemcitabine are used with DTCx materials.

The present invention attempts to a) bring the largest part of anticancer drug to contact with the tissue of the bladder wall and b) prolong the contact duration. These measures will probably improve the treatment efficacy.

The present invention provides sustained release materials that are efficient for indications such as the non-limited example of interstitial cystitis. The DTC material is designed to stay in the bladder for a week and the medical drugs used are a combination of Heparin and NSAID (Non-Steroidal Anti-Inflammatory Drug).

Prolonging the duration of tissue exposure to drug and significantly delaying the expelling of the drug from the bladder result in a dramatic improvement of the drug efficacy. The composition provided by the present invention, which furnishes a homogeneous, well-adhered coating of the bladder inner wall, has the capability to provide such prolonged drug release and overcome the difficulties of adherence to the internal wall of the bladder, such that the chemotherapy drug treatment duration is significantly prolonged and the cancer treatment efficacy is improved.

This solidified, unified and homogeneous layer coating of the bladder wall possesses numerous advantages. Foremost is the ability to continuously release anticancer agents over a prolonged period of time, as opposed to the gold standard treatment of introducing a fixed amount of drug for a short and indeterminate period, which is expelled from the bladder when the patient first urinates after the instillation induction.

A pre-clinical study of sows demonstrated a 20:1 higher level of chemotherapy in the bladder, six hours after instillation with the invented material compared to regular instillation of the same amount of chemotherapy.

Interestingly, the developed polymeric materials allow their comfortable administration through a thin tube, for example a urethral catheter, without exerting more than the common pressure required to inject a saline through such a device; and at the same time, as the liquid polymer settles upon the bladder wall, it solidifies creating a gelatinous film that then gradually releases the therapeutic ingredient upon said bladder wall.

This feature is of fundamental importance and is enabled by the fact that the polymeric composition was designed so as

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to possess reverse thermal gelling properties (see below), that is, to possess low viscosity at low temperatures (say, below 15° C.) and increase dramatically its viscosity as its temperature increases due to the body heat.

The coating layer created on the tissue of the internal cavity, disclosed in the present invention, is essentially a unified and homogeneous layer of substrate applied and affixed to organ tissue.

Beyond maximization of the area of the tissue that is exposed to drug, this coating can also be used to control the distance between organs. Following are several examples:

Fixation and treatment of pleura. A common condition in several lung and heart diseases is pleural effusion, when serous fluids, pus or chyle accumulate into the space between the visceral pleura and the parietal pleura layers surrounding the lungs—condition called hydrothorax or pleural effusion. Ordinarily there is little space between these layers, but certain malignancies may cause the accumulation of fluids at excessive levels that can impair breathing and cause severe outcome. A standard treatment for larger effusions is the insertion of intercostals drain, often accompanied by surgical pleurodesis—in which the two pleural surfaces are scarred to each other so that no fluid can accumulate between them—or even open pleuroctomy. This surgical joining of the layers is not always successful, but when it does—it is permanent.

A material of the present invention can be administered into the pleura cavity to adhere to the pleura layers and provide both a mechanical bond and sustained release of drug for treatment of the underlying malignancy (e.g. Tetracycline antibiotic for bacterial infection, or NSAID such as Naproxen to treat fever and inflammation. The pleura-hydrogel material is inserted into the pleura space via a catheter or trocar, as non-viscous liquid at a temperature that is below 15° C. and adheres to the surrounding tissue as it heats to body temperature. The material is designed to dissolve gradually into the pleura fluids over less than a week and both maintain mechanical support and release the drugs during that whole period. The main advantages of this method are the combination of this procedure ability to replace a more invasive one, the natural and easy application, the reduction of tissue damage, the soothing effect of the hydrogel and the enhanced healing effect of the sustained release of anti-inflammatory agents.

Fixation of organs and prevention of tissue adhesion in the abdomen during laparoscopy.

A material of the current invention can be introduced into the abdomen cavity and provide mechanical support to the target organs in the position that best fits the surgical procedure. The peritoneum-hydrogel material can be inserted into the peritoneum cavity via endoscope working channel, a catheter or trocar, as non-viscous liquid at a temperature that is below 15° C. and adhere to the surrounding tissue as it heats to body temperature. The material is designed to dissolve gradually into the pleura fluids over less than a week and both maintain mechanical support of the organs for several hours and release the drugs during a longer period.

Similar method, but with different materials can be used to prevent the adhesion of tissues between organs in the treated area, which may often occur during laparoscopic surgery.

The main advantages of this method are the combination of its ability to replace a more invasive procedure, the reduction of tissue damage, the soothing effect of the

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hydrogel and the enhanced healing effect of the sustained release of anti-inflammatory agents. A further advantage is the prevention of the need to remove the fixation surgically because of the natural degradation and expelling of the invented material from the treated area.

The release of drug from the admix/formulation/mixture occurs due to two phenomena that take place simultaneously after the gel is applied upon the bladder wall: (1) Drug diffusion from the gel to the aqueous medium (urine); (2) Dissolution of the gel itself in the aqueous medium. We may consider two extreme cases in which the drug either diffuses very fast from the gel to the urine medium, or diffuses very slowly. In the first case, the gel will be depleted very fast of drug so the bladder wall coated by the gel will "see" a low concentration of drug almost from the beginning. On the other hand, the concentration of drug in the urine will be higher and that is the concentration that uncoated parts of the bladder will see. If the case is the second (very slow release rate), the bladder wall coated by the gel will "see" a more or less high concentration of drug for a long time, in fact, until the whole of the gel is dissolved in the urine phase. These two separate but intertwined factors, which we call "two clocks", serve to design different therapies utilizing different drugs and tailor-made polymeric carriers according to the medical needs.

A water-based admix/formulation/mixture is made of large molecules that create spaces between the molecules that serve as matrix nodes. These spaces can be filled with drug molecules in a way that enables their diffusion into aqueous solution. The amount of drug molecules that can be held in a admix/formulation/mixture depends on the three-dimensional shape of the molecules as they are positioned in the admix/formulation/mixture. The diffusion rate depends on them admix/formulation/mixture three dimensional structure and packing factor.

DTCx materials are designed according to the three dimensional shapes of the admix/formulation/mixture and the compound molecules. admix/formulation/mixture design that uses even, large molecules, may store a high amount of drug, but will also enable fast diffusion out of the admix/formulation/mixture.

Admix/formulation/mixture design that combines larger and smaller molecules enables lower diffusion coefficients—leading to longer release durations—and, with some sacrifice of the included space volume.

Design of the admix/formulation/mixture that should store drugs for longer times is based on a 'matrix of polymer matrix'—i.e., higher order polymers. These structures can store drug molecules that start to diffuse only after the higher order structure is at least partially dissolved. Poloxamer 407 (PF-127) is a nonionic surfactant composed of polyoxyethylene—polyoxypropylene copolymers. In general, poloxamers are composed of white, waxy, freeflowing granules that are practically odorless and tasteless. The "F" designation refers to the flake form of the product. PF-127 is recognized as a pharmaceutical substance (Pharmacopeia/NF). It has a good solubilizing capacity, low toxicity and is therefore considered a good medium for drug delivery systems.

As described above, PF-127 is a commercially-available polyoxyethylene-polyoxypropylene triblock copolymer of general formula E106 P70 E106, with an average molar mass of 13,000. It is one of the series of poloxamer ABA block copolymers, whose members share the following chemical formula:

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PF-127 is more soluble in cold water than in hot water as a result of increased salvation and hydrogen bonding at lower temperatures. PF-127 aqueous solutions of 20 to 30% w/w have the interesting characteristic of reverse thermal gelation, i.e., they are liquid at refrigerated temperatures (4-5° C.), but gel upon warming to room temperature. The gelation is reversible upon cooling.

At low temperatures in aqueous solutions, a hydration layer surrounds PF-127 molecules. When the temperature is raised, the hydrophilic chains of the copolymer become desolved as a result of the breakage of the hydrogen bonds that had been formed between the solvent and these chains. This phenomenon favors hydrophobic interactions among the polyoxypropylene domains and leads to gel formation. Because of the dehydration process, the hydroxyl groups become more accessible. A liquid micellar phase is stable at low temperatures but transforms into the cubic structure by increasing the temperature. At higher temperatures, a phase of hexagonal packed cylinders is formed, as shown in FIG. 2.

Reverse thermal gelation and low toxicity have been the basis of research into the use of PF-127 as a possible drug delivery system in humans.

In a non-limiting example of DTCx materials in the context of the present invention, the hydrophilic character of the composition is an extremely important characteristic: It allows the polymer composition to gradually dissolve in the urine after the drug has been essentially released and the therapeutic session has been concluded without leaving foreign polymer composition residues inside the bladder.

The present invention's DTCx materials use a combination of polymers and drugs to obtain sustained release. Some of these materials have Reverse Thermal Gelation (RTG) property, thus can be injected as a free-flowing, low-viscosity liquid at low temperatures and form a gel upon exposure to body temperature. The DTCx materials present excellent rheology properties, high bio-adhesive capabilities in their gel state and high therapeutic efficacy. The present invention's DTCx materials soften in watery environment, such as exists in the bladder and will eventually dissolve. If needed, cooling the material inside the bladder with cold saline intravesical instillation will liquidize a DTCx material and wash it out of the bladder.

Materials to be utilized in the present application require a number of conditions to be fulfilled as follows:

- i. Sustained release of API. The materials can be tailored to release APIs for a pre-designed duration and according to a pre-designed profile.
- ii. Ability to insert material and coat through small orifices. Introducing DTCx materials into internal cavities requires good flow characteristics of the materials during insertion. One of the ways to get that capability is by using materials that act as 'plasticizer'—helping the material flow without significantly changing its viscosity and other rheology characteristics.
- iii. Adhesion and solidifying to internal surfaces for essentially pre-determined durations.

Some DTCx materials use polymers that have lower viscosities at low temperatures and gelate to high viscosities at body temperature. The gelling from low viscosity to high viscosity occurs at a specific temperature and produces mechanical tightening forces that enhance adhesiveness of the material to the tissue.

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The gelation temperature (gel point) is an important system parameter in the design of the insertion, spreading and adhesiveness system. The liquid DTCx material that enters the bladder has to be fixed and adhered to the bladder wall fast enough to prevent it from flowing under gravitational forces toward the lowest point in the bladder before it is fixated. In a non-limiting example, the specific formulation of the DTCx may contain NaCl (table salt) that can lower the gelation temperature and help in controlling the instillation process.

The determination of gel point is important both because of the fact that the gel's performance when applied in the body heavily depends on such parameter as well as due to the fact that it reflects the precise composition of the substance, thus constituting an important QC parameter to be measured in both R&D and production settings.

The determination of gel point for the above admixtures is essential since it is desirable that, in the context of the present invention, the gel point will not drop dramatically given that the lower the gelling temperature, the more difficult will be to inject the composition through a catheter into the body cavity.

Care should be taken concerning the active drugs that are used: In some cases, such as in Mitomycin C that is manufactured and distributed by Kyowa Ltd., salts are added to the drug (for volume complementation) and these salts change the viscosity—temperature dependence, so that the gelling point of the material is significantly lower. To avoid the lower gelling point, most DTCx materials use pure chemotherapy compounds, without added salts.

Flexibility to enable adherence through cycles of enlargement/reduction or flexing of muscles is an essential property of the material disclosed in the present invention. For example, the volume of the bladder when DTCx material is instilled is 100 ml and when it is naturally filled with urine—it can grow to 300 ml and even more. The present invention's DTCx materials are designed to withstand such extreme cycles of expansion and collapse.

A range of compounds may be utilized to formulate a composition that will render the required properties as described in this invention. Non-limiting example of specific compositions utilized in the present invention are stated below.

In preferred embodiments of the invention, the material comprises polymers and copolymers chosen from among the following: Polycarboxylic acids such as polyglycolic acid polylactic acid and polyacrylic acid; polyurethanes; polyesters such as poly(ethylene terephthalate); polyamides such as nylon; polyacrylonitriles; polyphosphazenes; polylactones such as polycaprolactone; polyanhydrides such as poly[bis(p-carboxyphenoxy)propane anhydride; polyethylene; polyvinyl chloride; ethylene vinyl acetate; Poloxamer block copolymers of the type PEGPPG-PEG; polyethylene oxide (polyethylene glycol); polypropyleneoxide (polypropylene glycol); polymethylacrylate; polysaccharides as dextrin, cyclodextrins, hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose, hydroxymethylcellulose, chitosan, polyvinyl alcohol and polyvinyl acetate; Polylactide (PLA) and Poly(Lactide-co-Glycolide) (PLGA); polymer microspheres; starch and modified starches; and cellulose polymers.

The medicament formulations according to the invention may comprise the active ingredient in dissolved, suspended and/or solid, amorphous or crystalline form. The active ingredient can be employed in various particle sizes, e.g. in unground, ground or in micronized form, to produce the admix/formulation/mixture according to the invention with controlled release of active ingredient.

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The admix/formulation/mixture described above with controlled release of active ingredient are for example in the form of active ingredient-containing hydrogels. These diffusion-controlled systems may be completely diluted in the hydrogel admix/formulation/mixture or can be multiparticulate, i.e. they may consist of a large number of coated cores such as, for example, of microencapsulated APIs, where appropriate together with conventional excipients and carriers, as defined below for example, is applied and subsequently coated with a diffusion coating which may comprise plasticizers and other excipients. The diffusion-controlled systems according to the invention may additionally consist of homogeneous active ingredient-containing cores which are produced for example by granulation, rotor granulation, fluidized bed agglomeration, tableting, wet extrusion or melt extrusion, where appropriate with spheronization, and are coated with a diffusion coating which may comprise plasticizers and other excipients. In a preferred embodiment of this invention, the active ingredient-containing particles comprise excipients such as, for example, acids or buffer substances which modify the pH and thus contribute to reducing the dependence of the release of active ingredient on the pH of the release medium. In a further preferred embodiment of this invention, the diffusion-controlled membrane comprises excipients which, through their pH-dependent solubility, influence the permeability of the membrane at different pH values and thus help to minimize the pH-dependence of the release of active ingredient.

The adhesive and thickening compounds preferably used in the production of coated neutral pellets (e.g. consisting of sucrose, microcrystalline cellulose, citric acid) are polycarbophil (polymer of acrylic acid crosslinked with divinyl glycol), hydroxypropylmethylcellulose (HPMC) and polyvinylpyrrolidone (PVP). It is likewise possible to employ other naturally, synthetic or partially synthetic polymers such as, for example methylcellulose (MC), hydroxy-propylcellulose (HPC), other hydroxyalkylcelluloses and hydroxyalkylmethylcelluloses, carboxy-methylcelluloses and salts thereof, polyacrylic acids, polymethacrylates, gelatin, starch or starch derivatives, as well as gums like guar gum and xanthan gum.

Bonding agents employed for the production of active ingredient-containing microcapsules are for example polycarbophil, cellulose, microcrystalline cellulose, cellulose derivatives such as, for example, HPMC, HPC and low-substituted hydroxypropylcellulose (L-HPC), dicalcium phosphate, lactose, PVP and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides (e.g. alginic acid, alginates, galactomannans) waxes, fats and fatty acid derivatives.

pH-modifying substances such as, for example, acids, bases and buffer substances are incorporated into the active ingredient-containing core. Addition of these substances makes it possible to reduce markedly the pH-dependence of the release of the APIs. Examples of suitable excipients which modify the pH in the active ingredient-containing cores are: adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, toluenesulphonic acid, trometamol, tartaric acid. Citric acid, succinic acid, tartaric acid, potassium hydrogen tartrate are preferably employed.

Particularly suitable for producing the diffusion coating are ethylcelluloses and polymethacrylates such as, for



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example, EUDRAGIT® NE, EUDRAGIT® RS and RL. However, other materials such as, for example, cellulose acetate and cellulose acetate butyrate can also be employed as film-forming diffusion-controlling polymers.

Examples of plasticizers used are citric acid derivatives (e.g. triethyl citrate, tributyl citrate, acetyl triethyl citrate), phthalic acid derivatives (e.g. dimethyl phthalate, diethyl phthalate, dibutyl phthalate), benzoic acid and benzoic esters, other aromatic carboxylic esters (e.g. trimellithic esters), aliphatic dicarboxylic esters (e.g. dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters), glycerol monoacetate, glycerol diacetate or glycerol triacetate, polyols (e.g. glycerol, 1,2-propanediol, polyethylene glycol of varying chain length), fatty acids and derivatives (e.g. glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol) and fatty acid alcohols (e.g. cetyl alcohol, cetylstearyl alcohol). The nature and amount of the plasticizer are chosen so that the above-defined release according to the invention and the necessary stability of the medicinal forms is achieved. The proportion of the plasticizer is from 0 to 50%, preferably 0 to 35%, particularly preferably 0 to 25% based on the mass of the hydrogel composition.

The release rate according to the invention is controlled by the gel composition. Certain components may increase the permeability of the admix/formulation/mixture including water-soluble polymers such as, for example, polyethylene glycols, PVP, PVA, HPMC, HPC, hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans or other soluble substances such as, for example, urea, salts (sodium chloride, potassium chloride, ammonium chloride, etc.), sugars (sucrose, lactose, glucose, fructose, maltose etc.), and sugar alcohols (mannitol, sorbitol, xylitol, lactitol, etc.). Based on the mass of the hydrogel, from 0 to 50%, preferably 0 to 35%, particularly preferably 0 to 20%, increasing permeability components may be employed.

A further aspect of the present invention are coated admix/formulation/mixture which comprise one or more swellable excipients which, on penetration of liquid through the membrane, swell greatly and, through the swelling and volume expansion, cause the coating to split. The splitting of the coating makes it possible for the medicinal substance to be released from the admix/formulation/mixture, usually in pulsatile form. Swellable excipients which these formulations may comprise are, for example, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC). Examples of suitable coating materials are cellulose acetate, ethylcellulose and polymethacrylates.

The described diffusion-controlled or pulsatile formulations can be employed directly and unmodified as medicinal form. However, they may also be further processed, where appropriate with addition of excipients, to the final admix/formulation/mixture. In order to achieve a desired release profile it is also possible to combine different coated formulations in one medicinal form, and administration of an initial dose can take place for example by combination with rapid-release formulation particles, e.g. uncoated pellets, granules or powder.

In a further embodiment of the admix/formulation/mixture according to the invention with controlled release there is use of formulations which include the active ingredient in a admix/formulation/mixture. These group of admixes/formulations/mixtures release the active ingredient by diffusion and/or erosion.

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The mass ratio of active ingredient to the total mass of the admix/formulation/mixture in these novel formulations is in the range from 1:1 to 1:1000, preferably in the range from 1:2 to 1:100.

Admixes/formulations/mixtures which can be employed are water-soluble, water-swellaable or water-insoluble substances. The novel formulations preferably comprise one or more water-swellaable polymers.

Preference is additionally given to medicinal preparations in the context of this invention which comprise water-soluble, hydrogel-forming polymers, these polymers having a nominal viscosity of at least 0.015 Pa s, preferably at least 0.050 Pa s (measured as 2% strength aqueous solution at 20° C.).

A preferred family of candidates to be utilized as a basis for obtaining said hydrogel is group of tri-block copolymers designated as PEG-PPG-PEG (PEG=Polyethylene glycol and PPG=Polypropylene glycol) and called Poloxamers, that produce reverse thermal gelation compositions, i.e., with the characteristic that their viscosity increases with increasing temperature up to a point from which viscosity again decreases. In particular, Poloxamer 407 possesses a gelling temperature which is above 10° C. but below the human body temperature, i.e., 37° C. This characteristic may confer the ability of a composition containing the compound to be injected or infused in liquid state into a bodily inner cavity at a low temperature and, afterwards, as the composition warms, it becomes a gel, thus stabilizing upon the wall of the inner human cavity.

This characteristic has allowed PF-127 to be used as a carrier for most routes of administration including oral, topical, intranasal, vaginal, rectal, ocular and parenteral routes. In recent years PF-127 has attracted particular interest in the design of dermal and transdermal delivery systems, with a view to promoting, improving or retarding drug permeation through the skin, bearing in mind that for topical delivery systems, accumulation in the skin with minimal permeation is desired, while for systemic delivery, the opposite behavior is preferred. Poloxamer 407 (PF-127) is a nonionic surfactant composed of polyoxyethylene-polyoxypropylene copolymers in a concentration ranging from 20-30%. At low concentrations ( $10^{-4}$ - $10^{-5}$ %) they form monomolecular micelles, but higher concentrations result in multimolecular aggregates consisting of a hydrophobic central core with their hydrophilic polyoxyethylene chains facing the external medium. Micellization occurs in dilute solutions of block copolymers in selected solvents above the critical micellar concentration, at a given temperature. At higher concentrations, above a critical gel concentration, the micelles can order into a lattice.

Aqueous solutions of poloxamers are stable in the presence of acids, alkalis, and metal ions. Commonly used poloxamers include the 88 (F-68 grade), 237 (F-87 grade), 338 (F-108 grade) and 407 (F-127 grade) types, which are freely soluble in water. The "F" designation refers to the flake form of the product. PF-127 has a good solubilizing capacity, low toxicity and is, therefore, considered a good medium for drug delivery systems. PF-127 is a commercially available polyoxyethylene-polyoxypropylene triblock copolymer of general formula E106 P70 E106, with an average molar mass of 13,000. It contains approximately 70% ethylene oxide, which accounts for its hydrophilicity. It is one of the series of poloxamer ABA block copolymers. As said above, PF-127 aqueous solutions of 20 to 30% w/w have the interesting characteristic of reverse thermal gelation, i.e., they are liquid at refrigerated temperatures (4-5° C.), but gel upon warming to room temperature. The gelation is reversible upon cooling. This phenomenon, therefore, suggests that when poured onto the skin

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or injected into a body cavity, the gel preparation will form a solid artificial barrier and a sustained release depot. Furthermore, PF-127 has been reported to be the least toxic of commercially available copolymers.

Water-soluble or water-swellaable matrix-forming polymers preferably employed are hydroxy-propylmethylcelluloses (HPMC), hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, other alkylcelluloses, hydroxy-alkylcelluloses and hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans such as, for example, guar and carob flour, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch or starch derivatives and mixtures of these substances.

In this connection, the admix/formulation/mixture according to the invention should preferably comprise at least 0.1-2.0% of a hydroxypropylmethylcellulose type whose nominal viscosity (measured as 2% strength aqueous solution at 20° C.) is at least 0.015 Pa s, preferably at least 0.050 Pa s. HPMC types preferably used have a degree of substitution of methoxy groups of 16.5-30%, particularly preferably 19-30%, and a degree of substitution of hydroxypropoxy groups of 4-32%, particularly preferably 4-12%.

In a particularly preferred embodiment of this invention, substances which control the pH in the admix/formulation/mixture are incorporated into the admix/formulation/mixture. The addition of such pH-modifying excipients and/or the addition of substances which dissolve or are dissolved out of the admix/formulation/mixture as the pH increases, and thus increase the porosity or permeability of the admix/formulation/mixture and/or promote erosion of the admix/formulation/mixture, makes it possible to achieve a virtually pH-independent release for these preferred embodiments of the present invention.

Examples of suitable excipients which can be added to the admix/formulation/mixture according to the invention to achieve release which is as far as possible pH-independent are the following substances: adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, cellulose phthalates, in particular cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate, cellulose succinates, in particular cellulose acetate succinate and HPMCAS, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, polymethacrylates (e.g. EUDRAGIT® types), toluenesulphonic acid, trometamol, tartaric acid. Citric acid, succinic acid, tartaric acid, HPMCAS, and polymethacrylates (e.g. EUDRAGIT® L) are preferably employed. If these excipients are present in the admix/formulation/mixture according to the invention, they are typically added in a proportion of from 10 to 50% based on the total mass of the admix/formulation/mixture.

Examples of plasticizing excipients in the hydrogel formulation are propylene glycol, glycerol, triethylene glycol, butanediols, pentanols, such as pentaerythritol, hexanols, long-chain alcohols, polyethylene glycols, polypropylene glycols, polyethylene/propylene glycols, silicones, phthalic acid derivatives (e.g. dimethyl phthalate, diethyl phthalate, dibutyl phthalate), benzoic acid and benzoic esters, other aromatic carboxylic esters (e.g. trimellithic esters), citric acid derivatives (e.g. triethyl citrate, tributyl citrate, acetyl triethyl citrate), aliphatic dicarboxylic esters (e.g. dialkyl adipates,

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sebacic esters, in particular diethyl sebacate, tartaric esters), glycerol monoacetate, glycerol diacetate or glycerol triacetate, fatty acids and derivatives (e.g. glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol), fatty acid alcohols (e.g. cetyl alcohol, cetylstearyl alcohol), sugars, sugar alcohols and sugar derivatives (e.g. erythritol, isomalt, lactitol, mannitol, maltitol, maltodextrin, xylitol). The concentration of plasticizers is normally from 0 to 30%, preferably from 0 to 20% based on the total mass of the gel.

Examples of suitable water-swellaable polymers which may be incorporated in the hydrogel are high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, low-substituted hydroxypropylmethylcellulose (L-HPC), poly(hydroxyalkyl methacrylate), alginates and galactomannans and mixtures thereof.

The present invention further relates to the combination of formulations with different release properties, e.g. rapid-release and slow-release, in one medicinal form.

The present invention also includes the use of the novel pharmaceutical admix/formulation/mixture for producing medicaments which are intended for the treatment and/or prevention of disorders in humans.

The non-limiting examples presented below illustrate the versatility that is provided by the diverse compositions, that allows its engineering to render different release profiles, flow characteristics, instillation temperatures, coating layer thickness and additional features as required by the specific treatment to be applied upon an internal cavity.

DTCx materials are inserted into the essentially empty bladder using a catheter. The material is inserted at low temperature in the range of 10° C to 100° C, where the material viscosity is low enough to be able to flow freely into the bladder. As the liquid material flows into the bladder it is naturally heated by the body temperature and eventually it reached that temperature. When the material temperature reaches the gelation temperature—it is passes from the liquid phase to viscous gel phase. The present invention's method is designed to ensure that material will cover essentially most of the surface of the bladder and that it will adhere to the bladder tissue at the point of contact.

In one preferred embodiment, a urinary catheter is used, such that incorporates a large balloon with a volume of 70 cc to 140 cc. The cold and liquid material is inserted into the bladder after the bladder was essentially emptied to minimize the amount of urine in the DTCx flow. The balloon is inflated to open the essentially collapsed bladder into an essentially symmetrical shape that is not less than a quarter of the volume of the bladder when it is filled with urine and reaches the volume that may cause urge to void (micturition).

In a preferred embodiment, the catheter system includes means to measure the momentary pressure that the balloon is applying on the bladder wall as indication for the physician to determine the level of inflating of the balloon. As a non-limited example, such means can measure the pressure of the liquid inside the balloon by connecting the supply tube into the balloon to a transparent column and reading the change in heights of liquid in that column as indication to the change in pressure on the bladder wall induced by inflating the balloon.

In a preferred embodiment, means are provided to make the flow out of the catheter exit from a hole positioned laterally close to the middle of the balloon.

In a preferred embodiment, means are provided to make the flow out of the catheter exit from the several holes set



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around the lateral middle of the balloon. The number of these exit holes can be between 2 and 4 holes. Means are provided to ensure that the catheter can be inserted into the urinary urethra in a known position, so that the position of each exit point is known. DTCx material is injected through the catheter in a number of doses that corresponds to the number of exit holes to control the overall distribution of the material around the balloon.

In a preferred embodiment each exit hole has a separate tube leading to it and each dose is injected into a separate tube, so that gelled material inside that tube does not disturb the flow of the next dose.

In a preferred embodiment, the position of the patient is changed for each dose so that each dose is injected separately between the inflated balloon and downward toward the bladder wall—to utilize gravitation to assist material flow.

In a preferred embodiment means are provided to apply pressure on the material during its heating and gelation to help enhance its fixation and adhesion to the mucosal tissue of the bladder wall. In one preferred embodiment, the pressure is applied by the large balloon that is filled with liquid such as water or saline. In another—the balloon can be filled with a heavier liquid such as saturated salt water (26%, with typical density of 1.2 g/ml), or saturated solution of glucose in water.

In another preferred embodiment, the balloon contains magnetic material embedded into its design; in another non-limiting example the catheter balloon can contain a metal rod. In yet another non-limiting example the balloon can be inflated with ferromagnetic liquid such as ferrofluids, made of finely divided magnetite (a form of iron oxide that is ferromagnetic), an oily carrier and a surfactant like the composition produced by FerroTec, Inc—see <http://www.ferrotec.com/products/ferrofluid/>. In this example, the pressure is applied by an external magnet that is pulled to the magnet inside the balloon. The external magnet can be a stationary magnet and the patient can be positioned against it corresponding to the exit hole that will be injected through. In another arrangement, the magnet can be rotated around the patient. In another embodiment, the procedure can be administered inside a system such as an MRI unit that enables rotating the magnetic field electronically.

In a preferred embodiment, the instillation of doses can be repeated with a similar or different set of materials to achieve a second layer of coating with additional properties, such as blocking layer that will reduce the diffusion of material into the bladder and slow the natural degradation of the material into the urine in the bladder. In a non-limiting example the similar materials can be the polymer ingredient of the DTC material such as a mixture of one or more of PEG-400, PEG-800 or Poloxamer with distilled water. In a nonlimiting example, this mixture can be less viscous than the DTC material used for the first layer, thus having a slower diffusion rate and providing a barrier against release of drug into the bladder volume.

Following the instillation, the coating will release active ingredients with medical effect on the bladder disease, such as cancer fighting drugs that affect bladder cancer tumors. In parallel that coating will naturally and gradually dilute into the bladder urine and be expelled during urination.

In case it may become needed to speed this process of gradual dilution by external actions, in a preferred embodiment, the coating can be removed promptly by cooling the coating below its gelation temperature, thus significantly lowering its viscosity and speeding its dilution into the bladder urine. In a non-limited example, the cooling can be affected by flushing the bladder with a flow of cold liquid such as water or saline through a regular catheter into the bladder.

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Water and Saline will also help to melt water-based DTCx gels. In another preferred embodiment, the flow of cold liquid can be applied via a special catheter, which will enable a thin or focused jet of liquid that will exert pressure on a small part of the coating. In a preferred embodiment, the direction of this jet may be changed such that it can be activated on several areas of the bladder coating sequentially.

In another preferred embodiment, speeding the removal of the coating can be achieved by applying a chemical agent such as a solvent that can assist in the dissolution of the coating. The chemical agent can be chosen according to the formulation of the DTCx. As a non-limiting example, ethyl or isopropyl alcohol and DMSO (dimethyl sulfoxide) can be used to dissolve coatings that include lipophilic materials.

The versatility of the polymer composition and the ability to control its physicochemical properties may allow the incorporation and optimize sustained-release dosing of additional active ingredients that may be desired in a chemotherapy treatment, including the reduction of pain, avoidance of inflammation and other undesired effects. Thus, besides the active ingredients that serve as chemotherapy agents, other drugs can be incorporated in the gel composition, among them anesthetic drugs (e.g., lidocaine), coagulants (e.g., pro-converin) anticoagulants (like heparin), anti-inflammatory drugs (steroidal and non-steroidal) and others, according to the medical requirements for patients suffering of SBC utilizing the effect of gradual release of the diverse active components for an optimal treatment.

According to another embodiment of the present invention, other drugs can be incorporated in the gel composition. Such drugs can be administered topically and can belong to at least one of the following families: Antineoplastic drugs; Chemotherapeutic agents; Anti-infective agents (Antimicrobial drugs, Antiparasitic agents, Antivirals); Drugs acting on the blood and blood forming organs (Antihemorrhagics, Anti-thrombotic agents, antianemic drugs); Dermatologic drugs (antifungals, antiseptic); Genito-urinary system drugs; Gastrointestinal system (antiobesity, acid related disorders); Metabolism drugs; Anti-inflammatory product; Musculoskeletal system acting drugs; Neurological drugs; Respiratory drugs; Cardio-vascular drugs; Otolological drugs; Anti-infective drugs; Corticosteroids drugs; Analgesics and anesthetics drugs; Antiparasitics drugs or any combination thereof.

According to another embodiment of the present invention, other drugs can be incorporated in the gel composition. Such drugs can be selected from a group consisting of, Antibacterials/Antibiotics, Antiinflammatories/Corticosteroids, Antineoplastics/Cytotoxics, Growth factors such as VEGF (Vascular Endothelial Growth Factor) and Inhibitory factors such as LIF (interleukin 6 class cytokine).

According to another embodiment of the present invention, at least one of the following is utilized in the admix/formulation/mixture: Poly (propylene oxide)—PPO, Poly (lactide-co-glycolic acid)—PLGA, Poly (N-isopropylacrylamide)—PNIPAM, Poly (propylene fumarate)—PPF, Poly (urethane)—PU, Poly (organophosphazene)—POP, Poloxamers of the type PEO-PPO-PEO (Poly (ethylene oxide), Poly (propylene oxide), Poly (ethylene oxide)) such as poloxamer 68, 88, 98, 108, 124, 127, 188, 237, 338 and 407, Stearic Acid, Poly (acrylic acid), Glyceryl Stearate, Cetearyl Alcohol, Sodium Stearoyl Lactylate, Hydroxy-Lenolin or any combination thereof.

According to another embodiment of the present invention the hydrogel/polymer composition may includes active pharmaceutical ingredients (APIs) that are expected to render a better therapeutic performance at lower risk levels. Specifically, the anticancerous drug mitomycin C (MMC) has been

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experimentally utilized in in vitro settings and applied on the internal bladder wall of animal specimens. The API is released in a controlled manner and the residence time inside the bladder is in the order of up to 24 hours instead of the accustomed 1-2 hours (until micturition).

According to another embodiment of the present invention the admix/formulation/mixture as provided above, can be used as biological glue so as to glue at least two tissues together. By adjusting the viscosity of the admix/formulation/mixture such biological glue can be provided.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein the weight of the balloon filled with a liquid denser than water is used for the application of the gel (utilizing its gravity).

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying force to said material further comprises a step of filling said catheter balloon with water and positioning the patient to utilize the gravitational forces directly toward the target tissue during the solidification of the material and cause optimal adhesion to that target tissue.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying gravitational force to said material further comprises a step of changing the position of the patient before applying partial doses of material to enable substantially full coating of the whole targeted internal cavity surface.

According to another embodiment, the material is used not only for coating internal cavities but rather coating organs selected from urinary bladder, mouth, nasal and paranasal sinus, gallbladder, esophagus, rectum, lungs, vagina, uterus, stomach, renal pelvis, pleura, abdomen, peritoneum, pelvis, liver, kidney, heart, intestine, brain, vertebral column, or any combination thereof.

In order better to illustrate how the invention may be put into practice, the following non-limiting examples of some of the embodiments of the invention are now provided.

## EXAMPLE 1

The effectiveness of the present invention hydrogel composition drug delivery to the urinary tract is demonstrated by the following pre-clinical example. Two embodiments of reverse thermal gelation, mucoadhesive and flexible hydrogel mixed with MMC (Kyowa) at a concentration of 1 and 2 mg/ml were prepared as follows.

DTC1: The material comprised Pluronic F-127 Ethylene Oxide/Propylene Oxide Block Copolymer (27.0%); Polyethylene glycol, average MW=400 (PEG-400) (1.0%); Hydroxypropylmethyl cellulose (HPMC) (0.2%); with the remainder water for injection (71.8%) was mixed with MMC (Kyowa) at a concentration of 1 mg/ml.

DTC2: The material comprised Pluronic F-127 Ethylene Oxide/Propylene Oxide Block Copolymer (27.0%); Polyethylene glycol, average MW=400 (PEG-400) (1.0%); Hydroxypropylmethyl cellulose (HPMC) (0.2%); with the remainder water for injection (71.8%) was mixed with MMC (Kyowa) at a concentration of 2 mg/ml.

DTC1 and DTC2 were intravesically instilled in pigs. The MMC concentration in tissue was measured using HPLC and compared to intravesical instillation of 1 mg/ml MMC in water (standard treatment of Non-Muscle Invasive Bladder Cancer; Total MMC dosage of 40 mg). In addition, bladder condition following instillation and in-vivo gel dissolution rate were evaluated. Higher MMC tissue concentrations were obtained following DTC1 and DTC2 hydrogels treatments in comparison to the standard control treatment (MMC in

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water). Two hours following intravesical treatment of DTC1 the MMC concentration in urothelium tissue was 11 fold higher for the DTC1 in comparison to that of the control treatment (1 mg/ml MMC in water). The MMC concentration following intravesical treatment of DTC2 was 1.8 fold higher than that obtained for TC-3+1 mg/ml MMC. MMC tissue concentration 6 hr following instillation of DTC1 was 13 fold higher than that of the control treatment. Similar average MMC concentrations were obtained for DTC1 and DTC2. No damages to the urothelium contiguity, or bladder wall perforation were observed. The ureters and urethras were intact. No sign of ureter or urethral obstruction was observed. No clinical effects on animal's vital parameter were detected during the complete treatment duration. In addition, residues of MMC hydrogel were observed in the pig bladder 6 hrs following instillation, supporting release duration of more than 6 hr.

## EXAMPLE 2

One embodiment of the material disclosed in the present invention (DTC-1) that incorporates the active therapeutic agent Mitomycin C (MMC) was prepared as follows. The material comprised Pluronic F-127 Ethylene Oxide/Propylene Oxide Block Copolymer (27.0%); Polyethylene glycol, average MW=400 (PEG-400) (1.1%); Hydroxypropylmethyl cellulose (HPMC) (0.2%); MMC (0.1%); with the remainder (71.6%) double distilled water. DTC-1 has an instillation temperature of 30° C.; a sustained release duration of 12 hours; and a degradation time (until fully expelled from the body) of <24 hours.

## EXAMPLE 3

A second embodiment of the material disclosed in the present invention (DTC-1) that incorporates the active therapeutic agent Mitomycin C (MMC) was prepared as follows. The material comprised Pluronic F-127 (27.0%); PEG-400 (1.1%); HPMC (0.2%); MMC (0.2%); with the remainder (71.5%) double distilled water. DTC-2 has an instillation temperature of 50° C.; a sustained release duration of 16 hours; and a degradation time (until fully expelled from the body) of <24 hours.

## EXAMPLE 4

A third embodiment of the material disclosed in the present invention (DTC-3) that incorporates the active therapeutic agent Valrubicin was prepared as follows. The material comprised Pluronic F-127 (27.0%); PEG-400 (1.1%); HPMC (0.3%); Valrubicin (0.1%); with the remainder (71.6%) double distilled water. DTC-3 has an instillation temperature of 50° C.; a sustained release duration of 18 hours; and a degradation time (until fully expelled from the body) of 18 hours.

The increase in the amount of HPMC reduces the release rate from the carrier composition.

The dominant release parameter will be the composition dilution in the urine medium. The therapeutic agent is gradually released during the time until the composition is totally expelled from the body.

## EXAMPLE 5

A fourth embodiment of the material disclosed in the present invention (DTC-4), designed to have faster release and expulsion rates and which incorporates the active thera-

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peutic agent MMC, was prepared as follows. The material comprised Pluronic F-127 (27.0%); PEG-400 (1.8%); HPMC (0.2%); MMC (0.1%); with the remainder (70.9%) double distilled water. DTC-4 has an instillation temperature of 30° C.; a sustained release duration of 10 hours; and a degradation time (until fully expelled from the body) of <16 hours.

The decrease in the amount of PEG-400 increases the release rate from the carrier composition and the composition's dilution in the urine medium. In this case, drug is released more rapidly and the composition is totally expelled from the body within 16 hours.

## EXAMPLE 6

A fifth embodiment of the material disclosed in the present invention (DTC-5) that incorporates lidocaine was prepared as follows. The material comprised Pluronic F-127 (27.0%); PEG-400 (1.8%); HPMC (0.2%); Lidocaine 25 mg/10 ml composition (0.25%); with the remainder (70.75%) double distilled water. DTC-5 has an instillation temperature of 60° C.; a sustained release duration of 24 hours; and a degradation time (until fully expelled from the body) of 24 hours.

## EXAMPLE 7

A sixth embodiment of the material disclosed in the present invention (DTC-6) that incorporates the therapeutic agent MMC was prepared as follows. The material comprised Pluronic F-127 (27.0%); PEG-400 (1.1%); HPMC (0.2%); MMC (0.25%); with the remainder (71.35%) double distilled water. DTC-6 has an instillation temperature of 30° C.; a sustained release duration of 18 hours; and a degradation time (until fully expelled from the body) of 24 hours.

## EXAMPLE 8

A seventh embodiment of the material disclosed in the present invention (DTC-7) that incorporates the therapeutic agent Gemcitabine HCl was prepared as follows. The material comprised Pluronic F-127 (25.0%); HPMC (0.2%); Gemcitabine HCl 25 mg/10 ml composition (0.25%); with the remainder (74. %) double distilled water. DTC-7 has an instillation temperature of 20° C.; a sustained release duration of 12 hours; and a degradation time (until fully expelled from the body) of <18 hours.

It should be clarified that the above compositions refer to the use of chemically pure drugs. Commercially, some of the drugs are provided as admixtures of the active ingredient and other non-active compounds. For example, MMC is provided commercially in ampoules that contain 0.1 mg MMC and 240 mg sodium chloride, which provide an isotonic solution when dissolved in 10 ml double distilled water. The presence of salts as sodium chloride in the final material may have a considerable effect in the composition's physicochemical properties, among them and not limited to viscosity and gelation temperature, which are critical in the application method. These filler materials must be considered when formulating the different compositions, which should be adapted to the actual formulation of the active ingredient and its excipients.

## EXAMPLE 9

An in-vitro study was performed to evaluate the efficacy of DTCx materials as cytotoxic agents in the urinary bladder. A carcinoma cell line was treated with MMC incorporated into the material disclosed in the present invention, and the results

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the treatment were compared to treatment with MMC dissolved in saline. Viability was assessed by MTT assay which tests mitochondrial function.

Cell lines of human bladder cancer were grown in RPMI 1640 medium, supplemented with FBS, 100 U/ml penicillin and 100 mg/ml streptomycin. At Day 1 cells were seeded in 24-well plates at a MMC concentration of  $1 \times 10^4$  (four replicates for each concentration, 1 plate for each analysis time). The cells were then exposed for 24 hours to DTC-2; in separate experiments, DTC-2 samples that contained 0.05, 0.1, 0.5 or 1 µg/ml MMC (Kyowa, Hakko Kogyo Co. Ltd.) were used. After 2 hours of incubation, medium was replaced with fresh medium for all plates.

The plates were tested by taking out the medium and adding fresh medium containing MTT reagent. All other plates were returned to the incubator for incubation of 24, 72, 120 and 144 h. MTT assays were used to assess toxicity at all time points. The proportion of living cells was calculated by comparison to the control vehicle.

A microplate reader (EL 312e: Bio-Tek Instruments, Winooski Vt.) was used to evaluate the presence of LDH as a color development measured by absorbance spectroscopy at 450 nm. Background optical density (OD) was subtracted from the OD readings of all samples. Cell viability was calculated by dividing the mean OD absorbance values of the treated wells by the mean OD absorbance of the control wells. All samples were tested in triplicate.

Reference is now made to FIG. 3, which shows graphs of cell viability as a function of time for various experiments. These results clearly demonstrate MMC cytotoxicity when different MMC concentrations are used in saline and in TC-2 respectively.

These studies clearly demonstrate that a dramatic effect may be observed in the case of 0.1 µg/ml (see FIG. 3A) where the difference between the effect of the DTC-2 hydrogel and that of the MMC-saline solution is most pronounced. For MMC-saline solution, there is practically no cell-kill, while with DTC-2 the cell-kill effect reaches 60%.

A direct relationship was demonstrated between MMC time of exposure and cytotoxicity. As seen in the graphs, in practically all cases the general trend is that the cytotoxicity increases as exposure time increases.

A direct relationship was also demonstrated between MMC concentration and cytotoxicity. Comparing the graphs obtained for different concentrations shows a higher cytotoxicity effect with the increase of concentration.

Thus, higher concentrations of MMC and longer exposure time contribute significantly to a higher cytotoxicity of MMC. When exposure time was increased from 2 hours to 24 hours, a cell kill level was achieved with less than one third of the MMC dose used for two hours exposure.

MMC concentrations in intravesical instillations have been evaluated in many different studies. Current treatment concentration is the highest that can be tolerated by the patient. Our results demonstrate that a further improvement in MMC efficacy can be gained by increasing the exposure time to MMC even at lower MMC concentrations.

## EXAMPLE 10

The inventors of the present invention conducted a pre-clinical trial with sick female mice model testing the DTCx material (TC-1 polymer and Gemzar chemotherapy) on a MBT-2 disease model. These tumors are extremely aggressive and resistant to chemotherapy therefore somewhat differ from human superficial bladder cancer. In this study, treatment was applied 14, 10, and 3 days following cell implan-



tation. Each group was divided into a DTCx material arm and a standard instillation arm consisting of Gemzar in saline, which served as control group. The results showed that the procedure was safe (indeed, with low mortality) and efficient, that is, consistent lower weights of cancerous bladder in the DTCx arm were obtained as compared to the control arm.

Large animal safety and efficacy studies were conducted on female pigs. The results demonstrated excellent control and no catheter-related or method-related adverse events.

The safety of the present invention's material and procedure by comparing the outcome of one week follow-up of animals following DTC-2 instillation to standard MMC instillation—seeking short & medium term adverse events (urinary retention, urethral obstruction, toxicity—both local and systemic).

Comparison of MMC concentrations in bladder tissue at 12 hours following instillation versus standard 2-hour instillation has demonstrated significantly higher MMC concentration in the bladder tissue for the procedure of the present invention, demonstrating the improved efficacy of the material and method disclosed in the present invention relative to methods known in the art for applying MMC to bladder tissue.

EXAMPLE 11

Studies performed by the inventors demonstrate that controlled release of the drug can be obtained which considerably prolong the actual contact between the bladder wall and the drug. This slow-release effect, which can take between 16 and 24 hours, dramatically increases such contact time and thus the continuous therapeutic effect of the drug upon the cancerous tissue. This effect, in tandem with the creation of an effective, stable coating upon the bladder wall, is expected to render a superior therapeutic effect in the treatment of bladder cancer.

In vitro studies performed by the inventors showed a gradual release of the drug embedded in the polymer composition in conditions similar to those of a human bladder (37° C., urine medium). The drug was gradually released throughout the tests over the course of 12-24 hours.

Further in vitro studies performed by the inventors show a gradual release of the drug embedded in the polymer composition in conditions similar to those of a human bladder (37° C., urine medium) when instead of continuously exposing the polymer composition to one portion of urine, such urine is changed every two hours and fresh portions replace the older ones during 24 hours. It was again found that the drug was gradually released throughout the tests during 16-24 hours.

A parallel set of in-vitro release experiments were performed using membraneless dissolution model: The hydrogel was loaded with the tested drug, layered in a glass containers, and equilibrated in the experimental temperature until homogenous gel layer was formed. acceptor solution was discarded every hour and replaced by a fresh solution. Drug concentration in acceptor solution was measured spectrophotometrically, gel dissolution was determined gravimetrically. Two examples are provided here.

a. Reverse thermal gelation hydrogel composed of Pluronic F-127 Ethylene Oxide/Propylene Oxide Block Copolymer (27.0%); Polyethylene glycol, average MW=400 (PEG-400) (1.0%); Hydroxypropylmethyl cellulose (HPMC) (0.2%); and the remainder water for injection (71.8%) was loaded with at a concentration of 10 mg/ml and 20 mg/ml Lidocaine hydrochloride.

The in vitro release of Lidocaine hydrochloride (10 and 20 mg/ml) from the hydrogel formulation enclosed above is

shown in FIG. 7. The released amount of Lidocaine hydrochloride was twofold higher for hydrogel loaded with 20 mg/ml Lidocaine hydrochloride in comparison to the hydrogel loaded with 10 mg/ml Lidocaine hydrochloride formulation. In addition, higher amount of Lidocaine hydrochloride was released from both formulations to the acceptor solution in the first testing time point (1 hr). The amount of Lidocaine hydrochloride released in the following time points was relatively constant.

b. Reverse thermal gelation hydrogel composed of Pluronic F-127 (20.0%); Pluronic F-68 (10.0%) Polyethylene glycol, average MW=400 (PEG-400) (1.0%); carboxymethyl cellulose sodium (CMC) (0.4%); and the remainder water for injection (68.8%) was loaded with at a concentration of 1 mg/ml cephalixin.

The in vitro release of cephalixin (1 mg/ml) from the hydrogel formulation enclosed above is shown in FIG. 7. The results demonstrate constant release of cephalixin at 3-6 hrs.

EXAMPLE 12

Studies were performed on the adhesiveness of the material of the present invention to mucosal tissue. Remarkable, unexpected results were obtained.

Adhesiveness was measured by the “rolling ball” method according to the ASTM D-3121-94 and PTSC-6 standard methods. In these experiments, the adhesiveness of the material disclosed in the present invention was compared to the adhesiveness of compositions disclosed in U.S. Pat. Nos. 6,207,180; 6,894,071; and U.S. Pat. Appl. US2006/0127210. The results indicate that the material is potentially suitable for use as a drug carrier for the treatment of bladder cancer. The results are summarized in Table 2 and show a difference of at least 20 times in adhesive power.

TABLE 2

Composition	Test 1 Result (cm)	Test 2 result (cm)
U.S. Pat. No. 6,207,180	32	20
U.S. Pat. No. 6,894, 017	>45	>28
U.S. patent application 2006/ 0127420	>45	>28
present invention	1.0	1.6

EXAMPLE 13

A second comparative study was performed in which the adhesiveness of the material of the present invention to biological material was compared with those of the three compositions cited in the previous example. The tests were performed according to ASTM standard D-2256-03, which determines adhesiveness by measuring peel strength. Adhesive properties were assessed applying equal amounts of the four compositions to biological tissues. Different types of loads were subjected to the samples, in order to mimic conditions occurring during in vivo applications. To standardize the test results, with respect to the multiplicity of applications and of tissues treated, pig bladder tissue was used as the unique substrate. The results are summarized in Table 3.



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TABLE 3

Composition	Adhesiveness (N/cm <sup>2</sup> )
U.S. Pat. No. 6,207,180	0.068
U.S. Pat. No. 6,894,017	0.047
U.S. patent application 2006/ 0127420	0.090
present invention	1.77

These results demonstrate that the material of the present invention is at least 20 times more adhesive to biological tissue than the materials known in the prior art.

## EXAMPLE 14

A second set of in vitro tests of the bioadhesive properties of the material disclosed herein was performed. These tests were performed on fresh female swine bladder using a TAXT2 texture analyzer according to the following protocol.

A tissue specimen was placed on a foam tape mounted onto the cylindrical support of the instrument (2 cm diameter and 4 cm length) and secured with a string. The whole support was then positioned at the top of the measuring system and held in place by a clamp. A given weight of hydrogel (for example, 0.5 g) was evenly poured onto another support of similar dimensions. The support was then affixed on the lower probe of the instrument. The two supports were aligned to ensure that the gel comes into direct contact with the surface of the swine tissue when the upper support is lowered. Measurements were performed at 25° C.

Before measurement, 100 µl of simulated urine fluid was evenly spread on the surface of the tissue. The upper support was then lowered at a speed of 0.5 mm/s to contact with the gel at a force of 1 N for a contact time of 10 s. It was then withdrawn at a rate of 1.0 mm/s to a distance of 10 mm. An acquisition rate of 200 points/s was chosen for the analysis. Data collection and calculation can be performed using the XTRA Dimension software package of the instrument. The work of adhesion and peak detachment force were used to evaluate the bioadhesive strength of the films. The work of adhesion is calculated from the area under the force-distance curve, and the peak detachment force is taken as the maximum force needed for detaching the film from the tissue. All measurements were performed in triplicate. The results are summarized in Table 4.

TABLE 4

Formulation	Pluronic F127	HPMC	PEG 400	Double Distilled Water	Work of Adhesion (mJ)	Peak Detachment Force (N)
A	25.0%	0.1%	0.5%	balance	0.51	3.34
B	27.0%	0.1%	1.0%	"	0.73	4.43
C	27.0%	0.2%	1.0%	"	1.13	6.35

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A marked increase in the bioadhesion strength was observed with an increase in HPMC content.

## EXAMPLE 15

Gel point measurements were made for a number of embodiments of the material herein disclosed. The general procedure for the measurements was as follows. First, 50 ml of the material was poured into a 100-ml glass container. A TEFLON-coated magnet of 2-2.5 cm length was then placed in the container. A thermocouple was then inserted into the bulk of the hydrogel. The container was placed in an ice bath on a magnetic stirrer plate. After the temperature of hydrogel dropped to 5° C., the ice bath was removed from the magnetic stirrer and the glass container containing the hydrogel was placed directly on top of the magnetic stirrer plate. The magnetic stirrer was then turned on and run at medium speed (120 rpm). The temperature was allowed to rise gradually (~1° C./min) to room temperature. The gel point for a particular measurement was recorded as the temperature at which the magnet stopped rotating. For each sample, the entire procedure was performed twice, and the gel point determined as the average of the two measurements.

The gel point was measured for three different embodiments of the material disclosed herein. The results of the measurements are summarized in Table 5.

TABLE 5

Formulation	Pluronic F127	HPMC	PEG 400	Double Distilled Water	Gel Point (° C.)
A	25.0%	0.1%	0.5%	balance	16.5
B	27.0%	0.1%	1.0%	"	14.1
C	27.0%	0.2%	1.0%	"	11.9

A further set of tests was performed in which MMC was incorporated into the material at a typical dosage concentration in order to determine the effect of the MMC (and its accompanying excipient) on the gel point of the final composition. Formulation D includes pure MMC; formulation E includes commercially obtainable MMC that includes 2 parts mannitol per 1 part MMC (for example, Boehringer Mannheim) and Formulation F includes 24 parts of sodium chloride per 1 part MMC (for example, Kyowa). The results are summarized in Table 6.

TABLE 6

Formulation	Pluronic F127	HPMC	PEG 400	MMC	NaCl	Mannitol	Double Distilled Water	Gel Point (° C.)
D	27.0%	0.2%	1.0%	0.1%	0	0	balance	11.8
E	27.0%	0.2%	1.0%	0.1%	0	0.2%	"	11.5
F	27.0%	0.2%	1.0%	0.1%	2.4%	0	"	5.1

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As can be seen, incorporation of NaCl into the commercial MMC significantly lowers the gel point while mannitol does not affect the gel point very much. The major drop in gel point produced by NaCl as compared to that of mannitol can be explained by (a) the fact that the concentration of NaCl is significantly larger and (b) NaCl is an inorganic salt, thus releasing a number of moles of ions that is twice the number of moles of the original NaCl. The drop in gel point due to the addition of MMC itself is insignificant for practical purposes.

In addition to the gelation point of the reverse thermal gelation hydrogel its viscosity as a function of temperature is an important feature that determines the hydrogel's behavior and ability to perform properly. Therefore the rheological properties of formulation candidates were studied. The viscosity vs temperature curves and values of Tg (gelling temperature) for each formulation were determined by RV DV III Brookfield rheometer and DVIII viscometer. The temperature at which a sharp increase in viscosity was obtained was determined as Tg. The viscosity measurement of the solid state of the gel (after complete solidification) was out of the range of the used rheometer and viscometer.

Reference is now made to FIG. 5, which presents a semi-logarithmic graph of viscosity as a function of temperature over a range of 5-35° C. for six different embodiments of reverse thermal hydrogels disclosed in the present invention composition for effective drug delivery (TCA, TCB, TCC, TCD, TCE, TCF), and Table 7, which presents the results of a sample gel point measurements.

TABLE 7

Formulation	Pluronic F127	Pluronic F68	HPMC	CMC	PEG-400	Gel Point
TCA	27.0%	—	0.2%	—	1.0%	15° C.
TCB	20.0%	—	0.2%	—	1.0%	22° C.
TCC	20.0%	10.0%	0.2%	—	1.0%	33° C.
TCD	25.0%	5.0%	0.2	—	1.0%	17° C.
TCE	20.0%	10.0%	—	0.4%	1.0%	—
TCF	20.0%	—	—	0.2%	1.0%	20° C.

This information is fundamentally important for the design and engineering of the hydrogel device since viscosity characteristics are critical in the gel flow through the catheter and spreading upon the bladder inner surface as it is injected by means of the catheter.

## EXAMPLE 16

One of the main features that determines the hydrogel's behavior and ability to perform properly is its viscosity as a function of temperature. Therefore the rheological properties of formulation candidates were studied, including viscosity as a function of temperature and determination of gelling temperature (Tg).

The viscosity vs temperature curves and values of Tg (gelling temperature) for each formulation were determined by means of an AR 1000-N Rheolyst rheometer (TA Instruments). The determination of Tg was determined through the crossover of the G' (elastic modulus) and G'' (viscous modulus) curves (see graph below the curves for TC-A).

Reference is now made to FIG. 5A, which presents a semi-logarithmic graph of viscosity as a function of temperature over a range of 4-50° C. for four different embodiments of the material herein disclosed (TCA, TCB, TCC, TCD), and to FIG. 5B, which presents the results of a sample gel point measurements. The formulations of the four embodiments are summarized in Table 8.

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TABLE 8

Formulation	Pluronic F127	HPMC	PEG-400	Gel Point
TCA	27.0%	0.2%	1.0%	11.9° C.
TCB	25.5%	0.2%	1.0%	14.5° C.
TCC	25.5%	0.15%	1.0%	14.8° C.
TCD	23.0%	0.15%	0.5%	22.3° C.

Interestingly, increase in viscosity with temperature in the low temperature range is approximately logarithmic. As can be seen in the graph, even minor modifications of the same basic formulation can produce substantial changes in the rheological behavior of the product.

For TC-A, the values of viscosity in the temperature range of interest are 16 Pa s at 10° C., which is the temperature at which the gel (which at that temperature is still in liquid form) is expected to be cooled before application upon the bladder wall; and 4,600 Pa s at 37° C., which is the gel's final temperature (body temperature). As explained below, the method utilized allowed the determination of the gel point as well.

This information is fundamentally important for the design and engineering of the catheter/hydrogel device since viscosity characteristics are critical in the gel flow through the catheter and spreading upon the bladder inner surface as it is injected by means of the catheter.

## EXAMPLE 17

According to another embodiment, the mixture of gels obtained, according to the present invention, adhere well to the inner surface of human cavities, by their inherent reverse thermal gelling properties. Furthermore, they release the drug in a controlled way and that they themselves (the gels) gradually degrade so that they are expelled from the body in up to 24 hrs.

The following are further examples of mixtures according to the present invention:

17.1—Vitamin gel for topical action provided, according to the following:

Vitamin (A, D or K) 0.05 %	12%
w/w Lecithin	
PEG 800	1%
Isopropyl stearate	8%
Pluronic F-127	20%
Double distilled water (DDW)	to 100%

17.2—Paclitaxel gel for cancer treatment, according to the following:

Paclitaxel	0.1%
Pluronic F-127	10.0%
Isopropyl Palmitate	1.0%
Lecithin	0.8%
Sodium Acryloyldimethyl-Taurate Copolymer	1.2%
Sorbic Acid	1.0%
Potassium Sorbate	0.1%
DDW	to 100%

17.3—Oral anesthetic gel, according to the following:

Lidocaine	1.0%
Pluronic F-127	27%
Ethoxyl diglycol	10%

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-continued

Lecithin	2.0%
Mint flavor	0.1%
DDW	to 100%

17.4—Anti-inflammatory composition, according to the following:

PEG-PLGA-PEG*	24.5%
HPMC	0.2%
PEG 400	0.5%
Ibuprofen	0.2%
DDW	to 100%

\*Ethylene glycol-lactic acid-co-glycolic acid-ethylene glycol triblock copolymer

17.5—Antibacterial gel, according to the following:

PEG 400	1.5%
PEG 1200	12.0%
Polysorbate 60	6%
Pluronic F-127	22%
Polyvinyl pyrrolidone-iodine complex	5.5%
DDW	to 100%

17.6—MMC gel, according to the following

Pluronic F-127	20%
Carboxymethyl cellulose sodium	0.5%
PEG 400	1%
MMC	0.2%
In 50 mM Tris-HCL buffer pH= 8	to 100%

17.7—Botox gel, according to the following

Pluronic F-127	20%
Carboxymethyl cellulose sodium	0.4%
PEG 400	1%
Botox	5U/gr
In 50 mM buffer acetate pH = 5	to 100%

## EXAMPLE 18

The effect of PEG-400 concentration on the gelation temperature was tested. The gelation temperature was determined at the temperature at which a sharp increase in the viscosity was observed (viscosity at gelation  $>10^6$  mPa s) in a Brookfield rheometer DV-III, spindle 52.

The results are summarized in Table 9.

TABLE 9

Formulation	HPMC	PEG-400	Pluronic F127	Gelation temperature (° C.)
a	0.2	1	27	15
b	0.2	10	27	6

## EXAMPLE 19

The effect of HPMC concentration on the gel viscosity was measured. Viscosity measurements were performed using a

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Brookfield rheometer DV-III, spindle 52, at 6° C., and represent the viscosity of the formulation in its liquid state. The results are summarized in Table 10.

TABLE 10

Formulation	HPMC (% w/w)	PEG-400 (% w/w)	Pluronic F127 (% w/w)	Viscosity (mPa s)
1	0.2	1	27	223
2	0.5	1	27	357
3	1.5	1	27	603
4	0.2	1	20	96
5	0.5	1	20	431
6	1.5	1	20	5742

## EXAMPLE 20

A gel composition according to the present invention was used for delivery of Mitomycin C (MMC) to pig bladder. MMC was incorporated into a gel containing 0.2% (w/w) HPMC, 1% (w/w) PEG-400, 27% (w/w) Pluronic F127 in water. In one experiment, the MMC concentration in the gel was 1 mg/ml (total dosage 40 mg); in another, the MMC concentration was 2 mg/ml (total dosage 80 mg). In each case, as a control, MMC was delivered from a solution containing MMC in the same concentration as in the analogous gel. The experimental results are summarized in FIG. 6.

As can be seen in the figure, higher MMC tissue concentrations were obtained following application of MMC contained in a gel of the present invention than by using a solution of MMC. Two hours following intravesical treatment by gel containing 1 mg/ml MMC, the MMC concentration in the tissue was 11 times higher than in the control. The MMC concentration in the tissue following application of gel with 2 mg/ml was 1.8 times higher than that in the experiment in which the concentration was 1 mg/ml. Six hours following treatment by gel containing 2 mg/ml MMC, the tissue MMC concentration was 13 times higher than in the control.

## EXAMPLE 21

An additional example for the effective drug delivery to the urinary tract of the present invention composition was demonstrated by a preclinical study testing the delivery of botulinum toxin A (BoNT-A) to rats bladder induced with chronic cystitis.

The effect of BoNT-A mixed with one embodiment of the invented material DTC-4 on bladder cystitis was demonstrated in a rat model (Sprague-Dawley) by comparing the effect of intravesical administration of BoNT-A in saline and in gel. The BoNT-A gel formulation (DTC-4) tested included 20U BoNT-A/ml gel composed of 27% Pluronic F127, 0.2% HPMC and 1% PEG-400 in water. Intravesical instillation of just DTC-4 and of saline with no botulinum toxin served as control groups. Chronic cystitis was induced by intraperitoneal injection of Cyclophosphamide (75 mg/kg was injected on day 1, 4 and 7). On day 2 PE-50 tubing was inserted into the rat bladder through the urethra. The bladder was emptied of urine and filled with DTC-4 or saline with and without BoNT-A (1 ml, 20 u/ml Allergan). On day 8 the animals were anesthetized and their bladders were examined by cystometrogram recording via PE-50 tube inserted into the bladder dome. After recovery the animals were gently restrained and the suprapubic catheter was connected to infusion pump (0.08 ml/min continuously) and pressure transducer for recording intravesical pressure and for saline infusion into the

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bladder to elicit repetitive voiding. The amplitude and the inter-contraction interval of reflex bladder contractions were recorded. Each tested groups included 2-4 rats.

The bladder contraction amplitude measured is shown in FIG. 4. The results demonstrate that following CYP administration the bladder contraction amplitude increased from 25-27 mmHg (contraction level for rat bladder with no hyperactivity) to about 42 mmHg. Following administration of BoNT-A in saline and in TC-3 gel to rats with induced chronic cystitis the contraction decreased to the baseline level amplitude of 30 mmHg and 24 mmHg, respectively. Better response was received for the BoNT-A in gel treatment demonstrating the activity of the BoNT-A in gel and efficacy of BoNT-A mixes with gel treatment.

Similar results were obtained for the measurements of bladder inter-contraction intervals summarized in FIG. 4. Following CYP administration the bladder inter-contraction intervals were shown to decrease from 4-5 min for rat administered with saline or gel to 2 min. Intravesical administration of BoNT-A in saline and in TC-3 gel to rats with induced chronic cystitis increased the inter-contraction intervals to about 4 min, close to the inter-contraction intervals for bladder with no hyperactivity. These results further support the activity of the BoNT-A in the gel and the efficacy of the BoNT-A mixes with gel treatment.

EXAMPLE 22

In order for the hydrogel formulation to be suitable for drug delivery in the bladder it must comply with the natural physiological changes in volume and shape i.e expansion during urine accumulation and contraction during urine voiding. During its the physiological function the bladder expands to about 5 times its original size. This property is tested for each hydrogel composition in the manner described hereof:

The flexibility of one embodiment of the reverse thermal gelation hydrogel (DTC1) for drug delivery was tested in vitro using sheep bladder tissue. To investigate the effect of tissue tension/expansion on hydrogel coverage, DTC1 stained with methylene blue was layered on top of a the mucosal side of rectangle section of bladder tissue with an area of 3\*3 cm. Following hydrogel gelation the tissue was starched and expanded by 3 fold to each direction (horizontally and vertically). The received area was 9 fold larger than the initial surface tissue area. The hydrogel coverage of the tissue following tissue expansion was examined. The hydrogel was shown to follow the stretched tissue. No gel detachment was observed.

EXAMPLE 23

An important feature that influences the hydrogel is its dissolution rate/erosion rate. Therefore dissolution properties of hydrogels disclosed in the present invention composition were studied.

The dissolution rate was determined using an in-vitro membrane free dissolution model at 37° C. In this model the gel is dissolved into the receptor medium (Dulbecco's phosphate buffer saline) which is carefully layered on top of a smooth and flat gel layer. The amount of gel dissolved is determined gravimetrically. After each sampling of the receptor medium it is carefully discarded and replaced by a fresh medium.

Reference is now made to FIG. 8, which presents the dissolution rate of six different hydrogels herein disclosed. The results demonstrate different dissolution rate of the various formulations tested. These various dissolution rates will

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determine the treatment duration following instillation of the drug loaded hydrogel. Hence, the reverse thermal gelation hydrogel composition for effective treatment of the urinary tract will be set based on the beneficial treatment duration for specific disease.

EXAMPLE 24

A further embodiment of the material disclosed in the present invention (DTC-11) is utilized upon organ linings consisting of serous tissue that does not possess a mucosal layer, in particular pleural and peritoneal walls. A condition common in several lung and heart diseases is pleural effusion, when serous fluids, pus or chyle accumulate into the space between the visceral pleura and the parietal pleura layers surrounding the lungs—condition called also hydrothorax. Certain malignancies enlarge the space between pleura layers and cause excessive levels of fluids to accumulate and impair breathing. Standard treatments for pleural effusions is the insertion of intercostals drain, often accompanied by surgical pleurodesis—in which the two pleural surfaces are scarred to each other so that no fluid can accumulate between them. Surgical joining of the layers is not always successful, but it is permanent.

A material of the present invention can be administered into the pleura cavity to adhere to the pleura layers and provide both a mechanical bond and sustained release of drug for treatment of the underlying malignancy (e.g. Tetracycline antibiotic for bacterial infection, or NSAID such as Naproxen to treat fever and inflammation).

The pleura-hydrogel material is inserted into the pleura space via a catheter or trocar, as non-viscous liquid at a temperature that is below 20° C. and adheres to the surrounding tissue as it heats to body temperature. The material is designed to dissolve gradually into the pleura fluids over less than a week and both maintain mechanical support and release therapeutic agents during that whole period.

This procedure can replace the more invasive pleurodesis with the additional benefits of tissue damage reduction, the soothing effect of the hydrogel and improved healing due to the sustained release of anti-inflammatory agents.

The following exemplary formulation can be applied (DTC11):

PEG-PLGA-PEG*	24.5%
HPMC	0.1%
PEG 400	0.4%
DDW	to 100%

\*Ethylene glycol-lactic acid-co-glycolic acid-ethylene glycol triblock copolymer

Said composition adheres well to said walls providing an effective matrix for the transport and release of therapeutic active ingredients. In particular, the admixture can carry anti-inflammatory drugs to be applied in case of pleural or peritoneal inflammation.

EXAMPLE 25

Fixation of organs and prevention of tissue adhesion in the abdomen during laparoscopy:

A material of the current invention can be introduced into the abdomen cavity and provide mechanical support to the target organs in the position that best fits the surgical procedure. The peritoneum-hydrogel material can be inserted into the peritoneum cavity via endoscope working channel, a catheter or trocar, as non-viscous liquid at a temperature that is



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below 15° C. and adhere to the surrounding tissue as it heats to body temperature. The material is designed to dissolve gradually into the pleura fluids over less than a week and both maintain mechanical support of the organs for several hours and release the drugs during a longer period.

Similar method, but with different materials can be used to prevent the adhesion of tissues between organs in the treated area, which may often occur during laparoscopic surgery.

The main advantages of this method are the combination of its ability to replace a more invasive procedure, the reduction of tissue damage, the soothing effect of the hydrogel and the enhanced healing effect of the sustained release of anti-inflammatory agents. A further advantage is the prevention of the need to remove the fixation surgically because of the natural degradation and expelling of the invented material from the treated area.

The following exemplary formulation can be applied (DTC-12):

PEG-PLGA-PEG*	24.5%
CMC	0.4%
PEG 400	0.4%
DDW	to 100%

EXAMPLE 26

A binary API system (DTC-13 to DTC-16) was formulated which allowed a different release profile from the same gel structure. The relative release rate from the basic formulation was controlled by the addition of changing amounts of the surfactant sodium dodecyl sulfate (SDS), which affected the overall lipophilic/hydrophilic balance of the formulation. The APIs in question were mitomycin C (MMC) and lidocaine. The following table presents the composition of three basic formulations and the release time of 80% of each of the two APIs. From an applicative point of view, it is of much interest to obtain a relatively rapid release of lidocaine, which produces the local anesthetic effect upon the organ tissue to be treated, followed by a slow release of the MMC, that may allow a superior chemotherapeutic treatment of said organ.

TABLE 11

DTC-16	DTC-15	DTC-14	DTC-13	MATERIAL
27.0	27.0	27.0	27.0	Pluronic F127 (%)
0.2	0.2	0.2	0.2	HPMC (%)
1.0	1.0	1.0	1.0	PEG-400 (%)
0.2	0.1	0.05	0	SDS (%)
71.6	71.7	71.75	71.8	DDW (%)
0.1	0.1	0.1	0.1	MMC (%)
1.0	1.0	1.0	1.0	Lidocaine (%)
12	14	15	16	Release time 80% MMC (hrs)
10	60	120	180	Release time 80% Lidocaine (min)

The results shown in table 11 demonstrate that adding a small amount of SDS dramatically affects the release profile of the two drugs respectively. This exemplifies, without limiting, the possibilities of engineering the gel composition in a way that allows two or more different APIs to release from the gel matrix each at their own pace—according to the treatment needs. In the example above, it may be desirable, for example, that the soothing effect of the lidocaine be felt by the patient rapidly, just before the MMC commences its own activity, that may be painful, and thus a rapid release of the lidocaine

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may be desired while a slow release of the same may be unfelt and this ineffective. On the other hand, one can conceive other treatments where a lower but more prolonged anesthetic effect be required, and thus the formulation will change accordingly. The possibilities are limitless as presented by the non-limiting examples above.

We claim:

1. A thermoreversible hydrogel, comprising:  
between 20% and 30% (w/w) of an ethylene oxide/propylene oxide triblock copolymer characterized by an average molar mass of 13000 and a general formula E106 P70 E106;  
between 0.05% and 0.3% HPMC;  
between 0.4 and 2.5% PEG-400;  
an effective amount of a therapeutic agent; and  
the balance water.
2. The thermoreversible hydrogel of claim 1, comprising:  
between 0.1% and 0.3% HPMC; and  
between 0.4 and 1.8% PEG-400.
3. A thermoreversible hydrogel, comprising:  
between 23% and 27% (w/w) of an ethylene oxide/propylene oxide triblock copolymer characterized by an average molar mass of 13000 and a general formula E106 P70 E106;  
between 0.1% and 0.2% HPMC;  
between 0.5% and 1% PEG-400; and  
the balance water.
4. The thermoreversible hydrogel of any one of claims 1, 2, or 3, further comprising at least one component selected from the group consisting of:  
adhesive and thickening compounds;  
at least one bonding agents selected from the group consisting of polycarbophil, cellulose, microcrystalline cellulose, cellulose derivatives, low substituted hydroxypropylcellulose (L-HPC), dicalcium phosphate, lactose, PVP and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides, fats and fatty acid derivatives and any combination thereof  
pH-modifying substances;  
at least one diffusion coating selected from the group consisting of ethylcelluloses and polymethacrylates, cellulose acetate, cellulose acetate butyrate and any combination thereof;  
plasticizers;  
at least one substance selected from swellable excipients group consisting of polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC) , cellulose acetate, ethylcellulose and polymethacrylates, high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, poly(hydroxyalkyl methacrylate), alginates, galactomannans, and any combination thereof;  
at least one substance chosen from the group of water soluble polymers consisting of polyethylene glycols, PVP, PVA, HPC, hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans urea, salts, sodium chloride, potassium chloride, ammonium chloride, sug-

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ars, sucrose, lactose, glucose, fructose, maltose, sugar alcohols, mannitol, sorbitol, xylitol, lactitol, and any combination thereof;

at least one substance chosen from matrix-forming polymers group consisting of hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, alkylcelluloses, hydroxy-alkylcelluloses hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch, starch derivatives and any combination thereof.

5. The thermoreversible hydrogel of claim 4, wherein the adhesive and thickening compounds are selected from the group consisting of polycarboxylic acid, crosslinked acrylic acid, divinyl glycol, polyvinylpyrrolidone (PVP), methylcellulose (MC), hydroxy-propylcellulose (HPC), other hydroxyalkylcelluloses, hydroxyalkylmethylcelluloses, carboxy-methylcelluloses and salts thereof, polyacrylic acids, polymethacrylates, gelatin, starch or starch derivatives, as well as gums like guar gum and xanthan gum and any combination thereof.

6. The thermoreversible hydrogel of 4, wherein: the pH-modifying substances are selected from the group consisting of acids, bases and buffer, adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, toluenesulphonic acid, trometamol, tartaric acid, and any combination thereof; and,

the plasticizers are selected from the group consisting of citric acid derivatives, triethyl citrate, tributyl citrate, acetyl triethyl citrate, phthalic acid derivatives, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, benzoic acid and benzoic esters, other aromatic carboxylic esters, trimellitic esters, aliphatic dicarboxylic esters, dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters, glycerol monoacetate, glycerol diacetate or glycerol triacetate, polyols, glycerol, 1,2-propanediol, polyethylene glycol of varying chain length, fatty acids and derivatives, glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol, fatty acid alcohols, cetyl alcohol, cetylstearyl alcohol and any combination thereof.

7. The hydrogel of any one of claims 1, 2, or 3, further comprising at least one component selected from the group consisting of poly(propylene oxide) (PPO), poly(lactide-co-glycolic acid) (PLGA), poly(N-isopropylacrylamide) (PNIPAM), poly(propylene fumarate) (PPF), polyurethane (PU), poly(organophosphazene) (POP), Poloxamers of the type (poly(ethylene oxide)/poly(propylene oxide)/poly(ethylene oxide)) (PEO-PPO-PEO), stearic acid, poly(acrylic acid), glyceryl stearate, cetearyl alcohol, sodium stearoyl lactylate, hydroxy-lanolin, and any combination thereof.

8. The thermoreversible hydrogel of any one of claim 1, 2, or 3, comprising an active pharmaceutical ingredient selected from the group consisting of antineoplastic drugs; chemotherapeutic agents; anti-infective agents, antimicrobial drugs, antiparasitic agents, antivirals; drugs acting on the blood and blood forming organs, antihemorrhagics, antithrombotic agents, antianemia drugs, dermatologic drugs, antifungals, antiseptics, genito-urinary system drugs, gastrointestinal sys-

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tem drugs, antiobesity drugs, drugs for treating acid related disorders, metabolism drugs, anti-inflammatory product, musculoskeletal system acting drugs; neurological drugs, respiratory drugs, gene therapy, cardio-vascular drugs, otological drugs, corticosteroids, analgesic and anesthetic drugs, growth factors, VEGF, inhibitory factors, LIF and any combination thereof.

9. The thermoreversible hydrogel of claim 8 wherein the active pharmaceutical agent is selected from the group consisting of Mitomycin C, Doxorubicin, Valrubicin, Gemcitabine, Thiotepa, Taxotere, Ethoglucid (Epodyl), Epirubicin, Pirarubicin, Apaziquone, Vicinium, Botulinum toxin, Fibrin, Lidocaine, Thrombin, Collagen, Naproxen and Ibuprofen.

10. A method for providing sustained-release topical treatment of a condition affecting an internal body cavity, comprising administering the hydrogel of claim 8 to the internal body cavity.

11. A method for providing sustained-release topical treatment of a condition affecting an internal body cavity, comprising administering the hydrogel of claim 9 to the internal body cavity.

12. The method of claim 10, wherein the internal body cavity is at least one selected from the group consisting of the urinary bladder, mouth, nasal and paranasal sinus, gallbladder, esophagus, rectum, lungs, vagina, uterus, stomach, renal pelvis, pleura, abdomen, peritoneum, pelvis, liver, kidney, heart, intestine, brain, vertebral column, and any combination thereof.

13. The method of claim 11, wherein the internal body cavity is at least one selected from the group consisting of the urinary bladder, mouth, nasal and paranasal sinus, gallbladder, esophagus, rectum, lungs, vagina, uterus, stomach, renal pelvis, pleura, abdomen, peritoneum, pelvis, liver, kidney, heart, intestine, brain, vertebral column, and any combination thereof.

14. The method of claim 10, wherein the hydrogel provides for parenteral administration of the active pharmaceutical ingredient.

15. A thermoreversible hydrogel, comprising: between 20% and 30% (w/w) of an ethylene oxide/propylene oxide triblock copolymer characterized by an average molar mass of 13000 and a general formula E106 P70 E106;

between 0.05% and 0.3% HPMC;

between 0.4% and 2.5% PEG-400;

an effective amount of a therapeutic agent selected from the group consisting of Mitomycin C, Doxorubicin, Valrubicin, Gemcitabine, Thiotepa, Taxotere, Ethoglucid (Epodyl), Epirubicin, Pirarubicin, Apaziquone, Vicinium, Botulinum toxin, Fibrin, Lidocaine, Thrombin, Collagen, Naproxen and Ibuprofen; and the balance water.

16. The thermoreversible hydrogel of claim 15, comprising:

between 0.1% and 0.3% HPMC; and

between 0.4% and 1.8% PEG-400.

17. The thermoreversible hydrogel of claim 15, comprising:

between 23% and 27% (w/w) of an ethylene oxide/propylene oxide triblock copolymer characterized by an average molar mass of 13000 and a general formula E106 P70 E106;

between 0.1% and 0.2% HPMC;

between 0.5% and 1% PEG-400; and

the balance water.

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18. The thermoreversible hydrogel of claim 15, further comprising at least one component selected from the group consisting of:

adhesive and thickening compounds;

at least one bonding agents selected from the group consisting of polycarbophil, cellulose, microcrystalline cellulose, cellulose derivatives, low substituted hydroxypropylcellulose (L-HPC), dicalcium phosphate, lactose, PVP and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides, fats and fatty acid derivatives and any combination thereof

pH-modifying substances;

at least one diffusion coating selected from the group consisting of ethylcelluloses and polymethacrylates, cellulose acetate, cellulose acetate butyrate and any combination thereof;

plasticizers;

at least one substance selected from swellable excipients group consisting of polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC), cellulose acetate, ethylcellulose and polymethacrylates, high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, poly(hydroxyalkyl methacrylate), alginates, galactomannans, and any combination thereof;

at least one substance chosen from the group of water soluble polymers consisting of polyethylene glycols, PVP, PVA, HPC, hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans urea, salts, sodium chloride, potassium chloride, ammonium chloride, sugars, sucrose, lactose, glucose, fructose, maltose, sugar alcohols, mannitol, sorbitol, xylitol, lactitol, and any combination thereof;

at least one substance chosen from matrix-forming polymers group consisting of hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, alkylcelluloses, hydroxy-alkylcelluloses hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids,

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polymethacrylic acid derivatives, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch, starch derivatives and any combination thereof.

19. The thermoreversible hydrogel of claim 15, wherein the adhesive and thickening compounds are selected from the group consisting of polycarbophil, crosslinked acrylic acid, divinyl glycol, polyvinylpyrrolidone (PVP), methylcellulose (MC), hydroxy-propylcellulose (HPC), other hydroxyalkylcelluloses, hydroxyalkylmethylcelluloses, carboxy-methylcelluloses and salts thereof, polyacrylic acids, polymethacrylates, gelatin, starch or starch derivatives, as well as gums like guar gum and xanthan gum and any combination thereof.

20. The thermoreversible hydrogel of 8, wherein: the pH-modifying substances are selected from the group consisting of acids, bases and buffer, adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, toluenesulphonic acid, trometamol, tartaric acid, and any combination thereof; and,

the plasticizers are selected from the group consisting of citric acid derivatives, triethyl citrate, tributyl citrate, acetyl triethyl citrate, phthalic acid derivatives, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, benzoic acid and benzoic esters, other aromatic carboxylic esters, trimellithic esters, aliphatic dicarboxylic esters, dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters, glycerol monoacetate, glycerol diacetate or glycerol triacetate, polyols, glycerol, 1,2-propanediol, polyethylene glycol of varying chain length, fatty acids and derivatives, glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol, fatty acid alcohols, cetyl alcohol, cetylstearyl alcohol and any combination thereof.

21. The hydrogel of claim 15, further comprising at least one component selected from the group consisting of poly(propylene oxide) (PPO), poly(lactide-co-glycolic acid) (PLGA), poly(N-isopropylacrylamide) (PNIPAM), poly(propylene fumarate) (PPF), polyurethane (PU), poly(organo-phosphazene) (POP), Poloxamers of the type (poly(ethylene oxide)/poly(propylene oxide)/poly(ethylene oxide) (PEO-PPO-PEO), stearic acid, poly(acrylic acid), glyceryl stearate, cetearyl alcohol, sodium stearyl lactylate, hydroxylanolin, and any combination thereof.

22. The method of claim 11, wherein the hydrogel provides for parenteral administration of the active pharmaceutical ingredient.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 9,040,074 B2  
APPLICATION NO. : 13/553198  
DATED : May 26, 2015  
INVENTOR(S) : Asher Holzer et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

**In the Specification**

In Column 32, Line 20, please delete the following: "E106 P70 E106" and replace with: --E101 P56 E101--

In Column 37, Line 64, please delete the following: "E106 P70 E106" and replace with: --E101 P56 E101--

In Column 42, Line 59, please delete the following: "E106 P70 E106" and replace with: --E101 P56 E101--

**In the Claims**

In Claim 1 at Column 62, Lines 11-12, please delete the following: "E106 P70 E106" and replace with: --E101 P56 E101--

In Claim 3 at Column 62, Lines 23-24, please delete the following: "E106 P70 E106" and replace with: --E101 P56 E101--

In Claim 15 at Column 64, Lines 44-45, please delete the following: "E106 P70 E106" and replace with: --E101 P56 E101--

In Claim 17 at Column 64, Lines 63-64, please delete the following: "E106 P70 E106" and replace with: --E101 P56 E101--

Signed and Sealed this  
Sixteenth Day of July, 2019



Andrei Iancu  
*Director of the United States Patent and Trademark Office*



# **EXHIBIT B**



US009950069B2

(12) **United States Patent**  
**Holzer et al.**(10) **Patent No.:** **US 9,950,069 B2**(45) **Date of Patent:** **\*Apr. 24, 2018**(54) **MATERIAL AND METHOD FOR TREATING  
INTERNAL CAVITIES**(71) Applicant: **UroGen Pharma Ltd.**, Raanana (IL)(72) Inventors: **Asher Holzer**, Raanana (IL); **Dorit Daniel**, Raanana (IL); **Michael Mullerad**, Tel Aviv (IL); **Jaime De La Zerda**, Haifa (IL); **Uri Shpolansky**, Pardes Hana (IL); **Nadav Malchi**, Pardes Hanna-Karkur (IL); **Yosh Dollberg**, Raanana (IL); **Dor Tal**, Hadera (IL); **Yossi Yavin**, Mikhmoret (IL); **Marina Konorty**, Hertzylia (IL)(73) Assignee: **UROGEN PHARMA LTD.**, Raanana (IL)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/366,256**(22) Filed: **Dec. 1, 2016**(65) **Prior Publication Data**

US 2017/0112935 A1 Apr. 27, 2017

**Related U.S. Application Data**

(63) Continuation of application No. 14/720,676, filed on May 22, 2015, which is a continuation of application No. 13/553,198, filed on Jul. 19, 2012, now Pat. No. 9,040,074, which is a continuation-in-part of application No. PCT/IL2011/000069, filed on Jan. 20, 2011.

(60) Provisional application No. 61/509,654, filed on Jul. 20, 2011, provisional application No. 61/296,589, filed on Jan. 20, 2010.

(51) **Int. Cl.****A61K 47/34** (2017.01)  
**A61K 47/38** (2006.01)  
**A61K 9/06** (2006.01)  
**A61K 31/407** (2006.01)  
**A61K 31/704** (2006.01)  
**A61K 31/167** (2006.01)  
**A61K 31/7068** (2006.01)  
**A61K 47/26** (2006.01)  
**A61K 31/07** (2006.01)  
**A61K 31/59** (2006.01)  
**A61K 31/122** (2006.01)  
**A61K 31/337** (2006.01)**A61K 9/00** (2006.01)**A61K 31/192** (2006.01)**A61K 31/79** (2006.01)**A61K 38/48** (2006.01)(52) **U.S. Cl.**CPC ..... **A61K 47/34** (2013.01); **A61K 9/006** (2013.01); **A61K 9/0024** (2013.01); **A61K 9/0034** (2013.01); **A61K 9/006** (2013.01); **A61K 31/07** (2013.01); **A61K 31/122** (2013.01); **A61K 31/167** (2013.01); **A61K 31/192** (2013.01); **A61K 31/337** (2013.01); **A61K 31/407** (2013.01); **A61K 31/59** (2013.01); **A61K 31/704** (2013.01); **A61K 31/7068** (2013.01); **A61K 31/79** (2013.01); **A61K 38/4893** (2013.01); **A61K 47/26** (2013.01); **A61K 47/38** (2013.01); **C12Y 304/24069** (2013.01)(58) **Field of Classification Search**

None

See application file for complete search history.

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Technical Bulletin, Pluronic® Block Copolymer NF Grades (Poloxamer NF Grades), BASF The Chemical Company, 2004, 2 pages.

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Primary Examiner — Jake Vu

(74) Attorney, Agent, or Firm — Cooley LLP

(57) **ABSTRACT**

A hydrophilic biocompatible sustained-release material is disclosed. The material comprises amounts of Pluronic F-127, PEG-400, HPMC and water, effective to produce a composition of sufficiently low viscosity at room temperature to be injectable into an internal body cavity via a tube inserted within a urinary catheter. At body temperature, the material exhibits a much higher viscosity and will stably adhere to the internal surface of a body cavity. As the material dissolves, a therapeutic agent incorporated therein is slowly released to the body cavity, while the material itself is excreted from the body.

**30 Claims, 8 Drawing Sheets**

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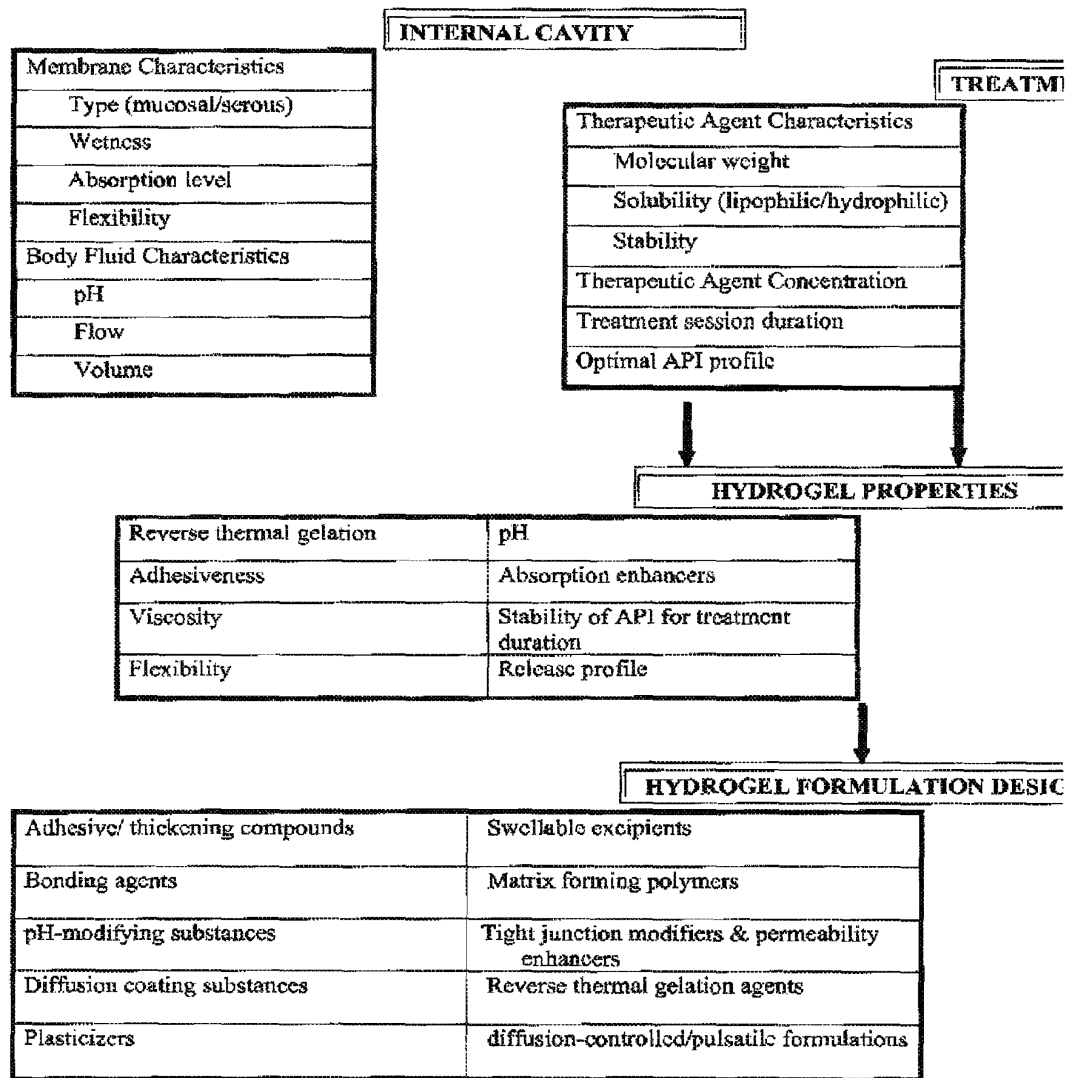


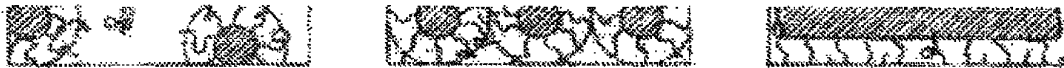
FIG. 1

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**Sheet 2 of 8**

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**FIG. 2**  
**(prior art)**



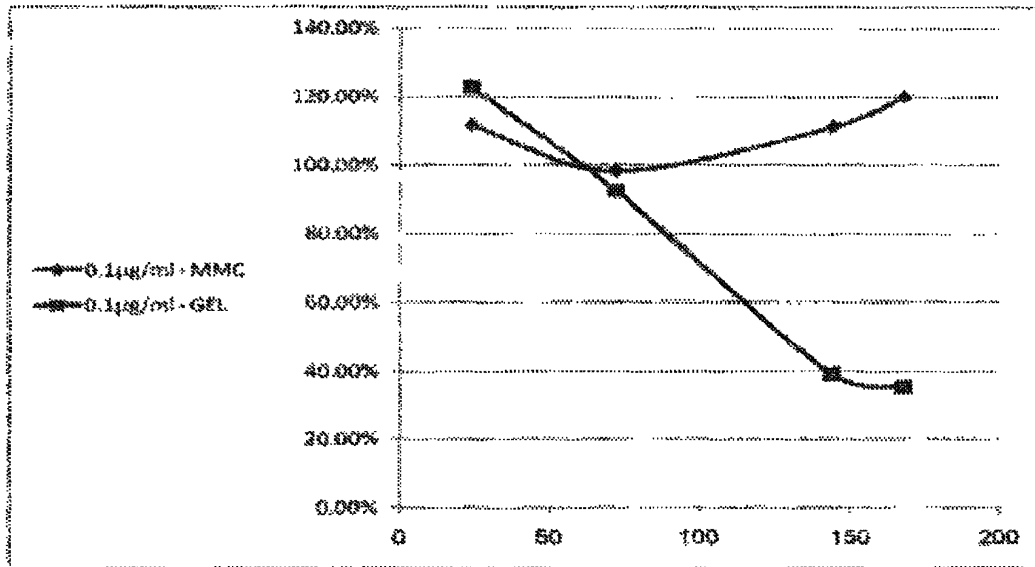


FIG. 3A

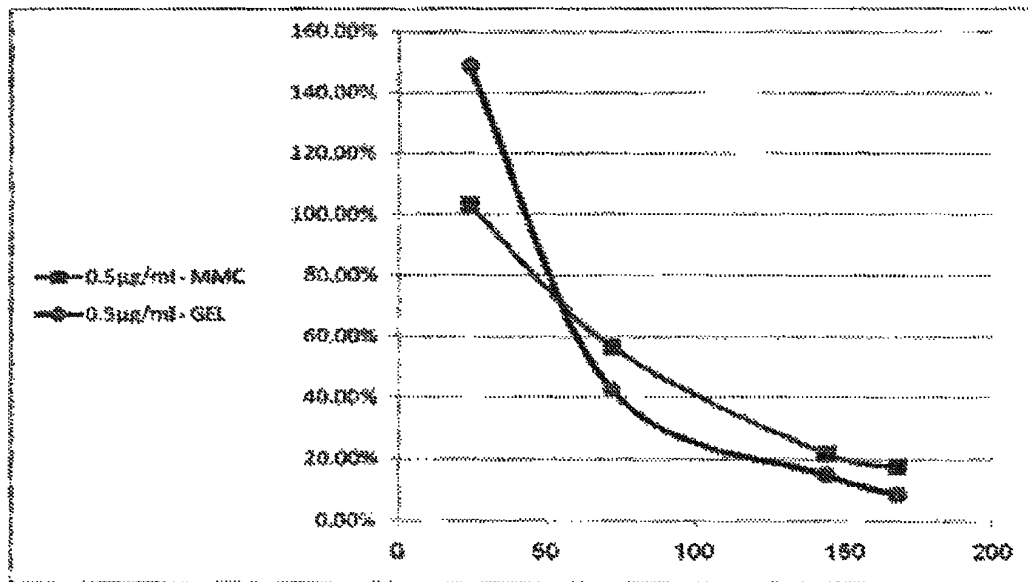


FIG. 3B

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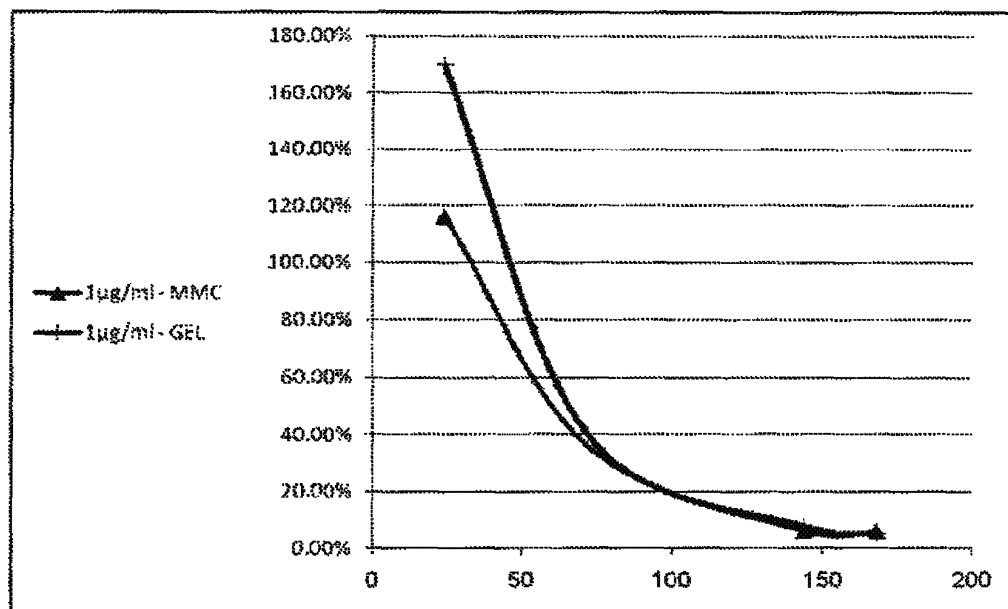


FIG. 3C

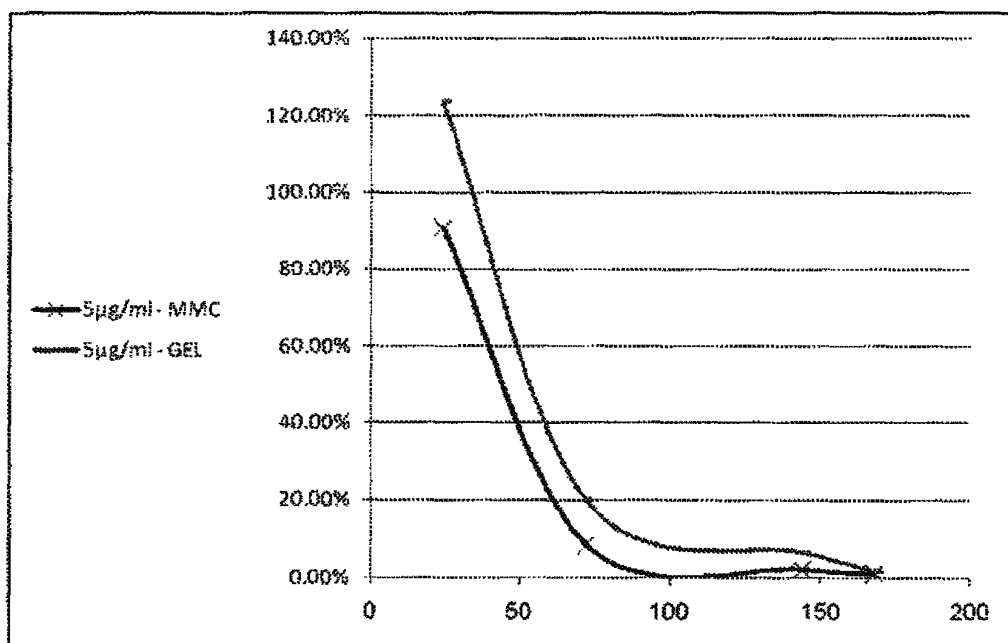


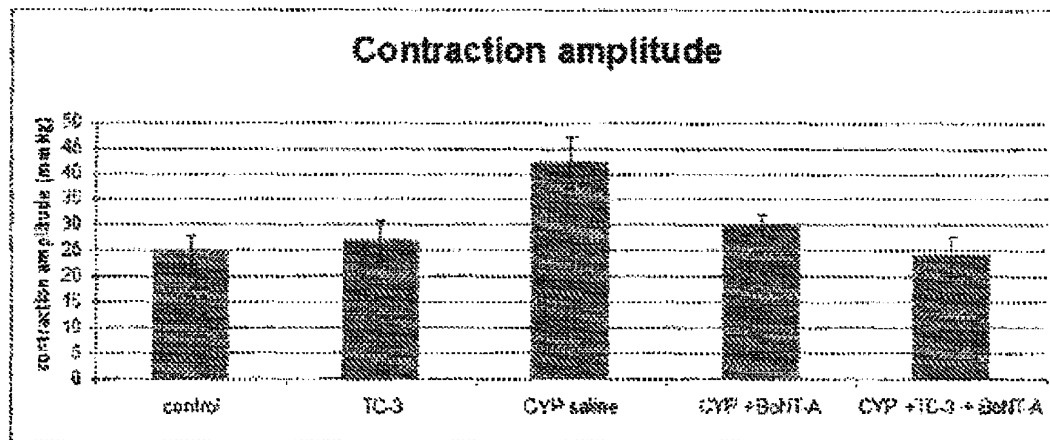
FIG. 3D

**U.S. Patent**

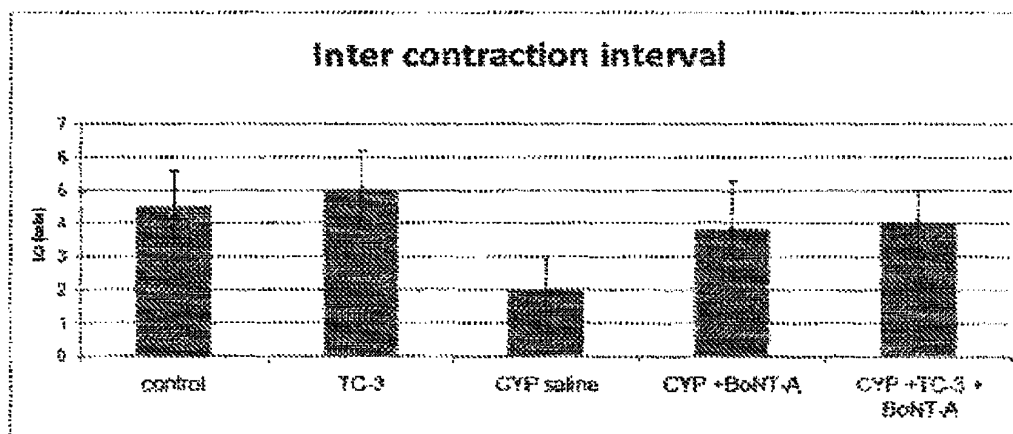
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**FIG 4A**



**FIG 4B**

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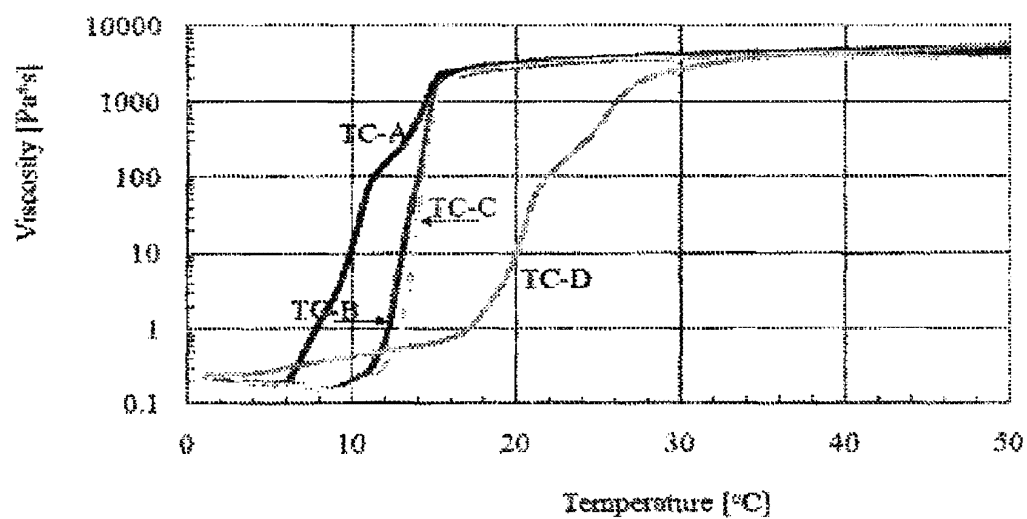


FIG. 5A

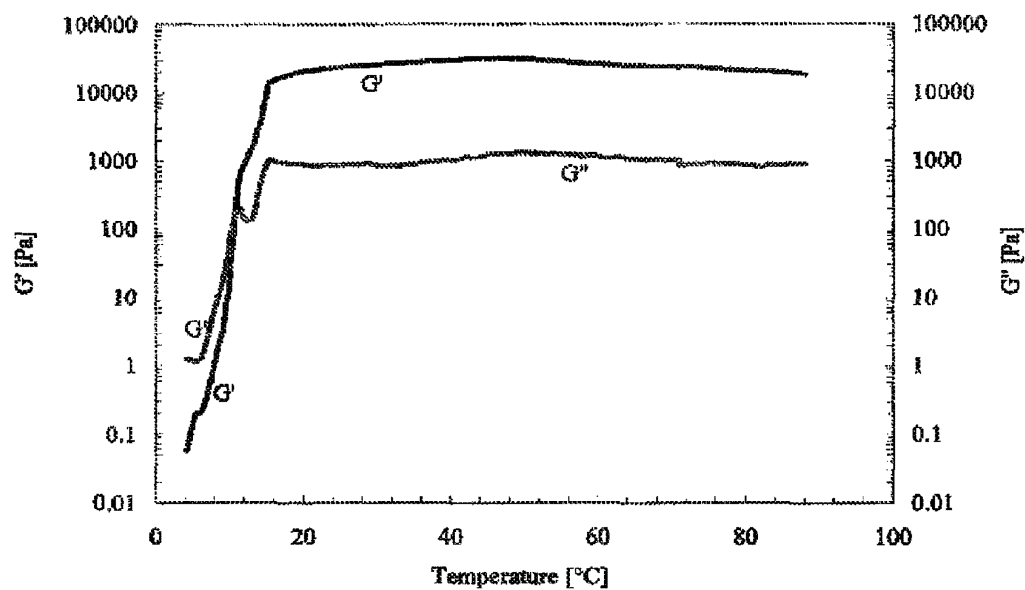


FIG. 5B

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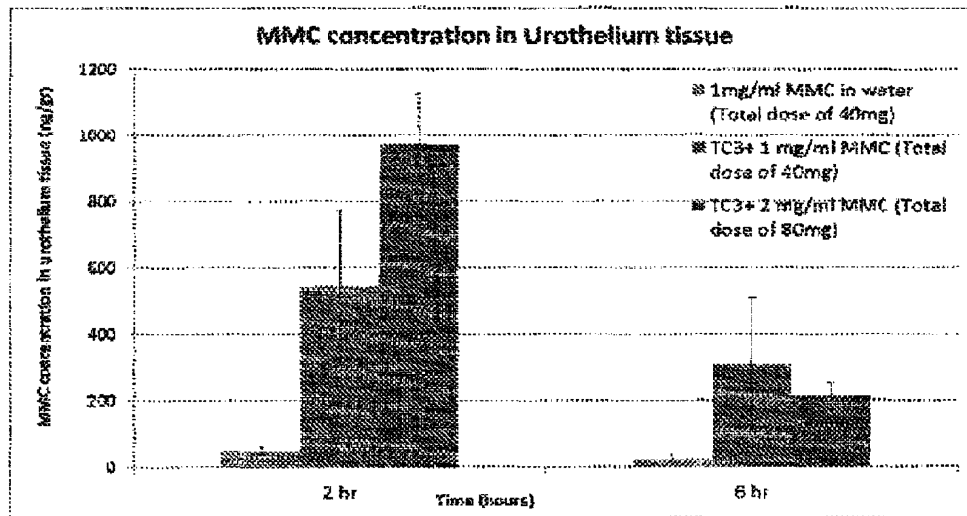


FIG. 6

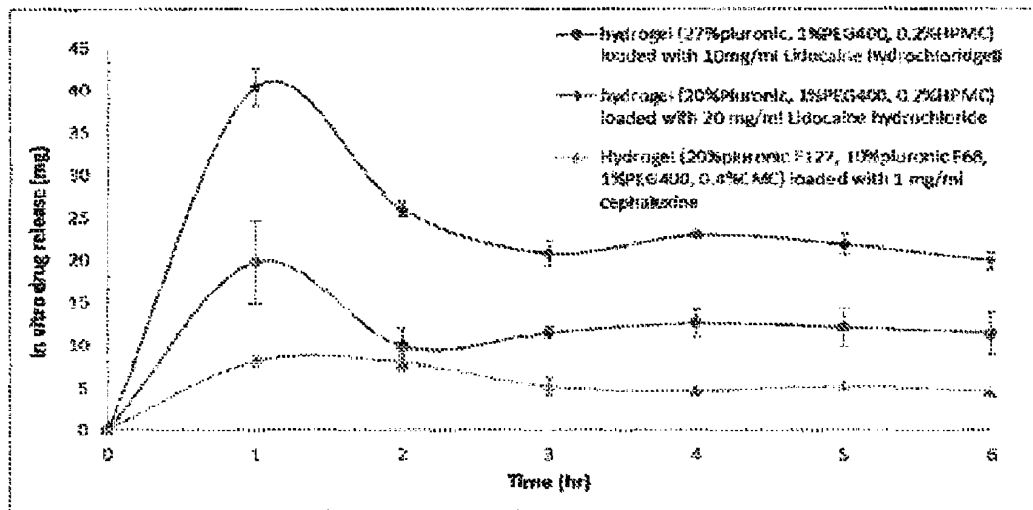


FIG. 7



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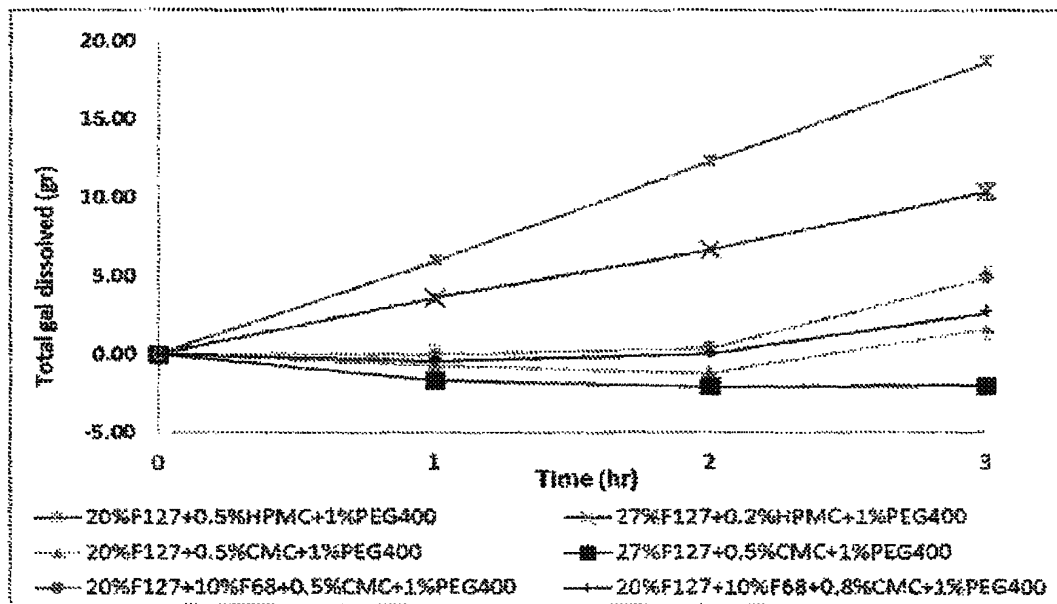


FIG. 8

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**MATERIAL AND METHOD FOR TREATING  
INTERNAL CAVITIES**

## REFERENCE TO RELATED APPLICATIONS

This application is a Continuation of U.S. application Ser. No. 14/720,676, filed May 22, 2015, which is a Continuation of U.S. application Ser. No. 13/553,198, filed Jul. 19, 2012, and granted, May 26, 2015, as U.S. Pat. No. 9,040,074, which is a Continuation in Part of International Application No. PCT/IL2011/00069, filed Jan. 20, 2011, which claims the benefit of U.S. Provisional Application Ser. No. 61/296,589, filed on Jan. 20, 2010. U.S. application Ser. No. 13/553,198, filed Jul. 19, 2012, also claims the benefit of U.S. Provisional Application Ser. No. 61/509,654, filed on Jul. 20, 2011, all of which are hereby incorporated by reference in their entireties.

## FIELD OF THE INVENTION

The invention relates in general to materials, means and methods for sustained release of therapeutic agents for topical treatments. It relates in particular to means and methods for topical treatment of diseases of internal body cavities by embedding therapeutic agents in a slowly degrading biocompatible mixture applied to affected tissue.

## BACKGROUND OF THE INVENTION

## i. Internal Cavities

Internal body cavities (e.g., cavities within the body accessible through a body orifice or via image guided laparoscopic methods) contain organs that when diseased may benefit from prolonged topical exposure to certain drugs. These cavities are naturally wet and are either continuously flushed or generate a flow of body fluids, such as urine, serous fluids or lymphatic fluids—that contribute to gradual expelling of treatment materials.

Many cavities are characterized by their internal natural movement—due, for example, to body motion or peristaltic motion—that constantly changes their shape.

The tissue in all internal cavities in the body is composed of only three basic types of tissue: epithelial, connective and muscular. Almost all epithelial cells, rest on connective tissue, the lamina propria, which support the epithelium and provides nutrition and binds to neighboring structures. The common types of covering epithelia can have either simple, pseudo-stratified or stratified cell structure. The epithelia of vessels and serous cavities are squamous, but many other cavities have epithelia cell structure that is either cuboidal or columnar, which provide good mechanical protection and good ability to achieve adhesion. The mouth, esophagus, larynx, vagina and anal canal have a non-keratinized cell structure to maintain wetness and are more challenging for adhesion. The urinary tract has similar, but transitional cell structure, that provides stretching, mechanical strength and strongest resistance to adhesion of materials.

Several common tissue properties affect the requirements for targeted delivery materials:

- wetness of the cavity lining tissue
- mechanical composition and consistency
- absorption capability
- expansion and movement characteristics of the internal cavities or attached organs
- existence of body fluids for expelling the delivery materials

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## ii. Topical Treatment of Diseases

The method by which a drug is delivered can have a significant effect on its efficacy. In many cases, the drug is introduced into the blood system, which then delivers it via the blood stream throughout the body. This form of access is broadly termed systemic treatment. In other cases, a more targeted delivery can focus the therapeutic effect onto the target organ, providing therapeutic benefits and avoiding side effects. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. In the context of the present invention, treatments that effect specific tissues or organs by directly accessing them are termed topical treatments, as opposed to systemic treatments that were described above. Sustained release of a drug involves polymers that typically release the drug at a controlled rate due to diffusion out of the polymer or by dilution of the polymer over time. Topical administration of drugs changes the rate at which drugs enter the tissue and the pharmacokinetics of the drug, thus the correctly designed materials can optimize the therapeutic effect by controlling the drug release rate. Since all internal organ tissue is water-based, administering drugs in water-based solutions is optimal.

## iii. Topically Administered Drugs

Among the drugs that can be administered topically are drugs that belong to the following families:

1. Antineoplastic drugs
2. Chemotherapeutic agents
3. Anti-infective agents (e.g. Antimicrobial drugs, Antiparasitic agents, Antivirals)
4. Genito-urinary system drugs
5. Anti-inflammatory products
6. Analgesics
7. Musculoskeletal system acting drugs
8. Drugs acting on the blood and blood forming organs (Antihemorrhagics, Antithrombotic agents, antianemic drugs)
9. Dermatologic drugs (antifungals, antiseptic)
10. Gastrointestinal system (antiobesity, acid related disorders)
11. Metabolism drugs
12. Neurological drugs
13. Respiratory drugs including nasal drugs
14. Cardio-vascular drugs
15. Otolological drugs
16. Anti-infective drugs
17. Corticosteroids drugs
18. Analgesics drugs
19. Antiparasitics drugs
20. Anesthetic Drugs

In other cases, the topical treatment is just evolving:

21. Growth factor (e.g., for treatment of heart muscle ischemia)

## 22. Gene Therapy agents

In other cases, the topically administered material has medical effect without actually being considered an active pharmaceutical ingredient:

23. Mucin
24. Hyaluronic Acid

Besides their therapeutic effect, drugs are classified according to their chemical and physical properties and thus constitute families of compounds that, due to their common similar characteristics, fit particular drug vehicles. Some of those properties include:

- Lipophilicity or hydrophilicity
- Molecular weight and physical size
- Diffusability through different media which is hydrophobic, hydrophilic, viscose, etc.
- Solubility

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## iv. Physical Characteristics of Internal Cavities

The effectiveness of application of a topical therapeutic agent to a specific internal cavity will depend on the physical characteristics of the inner tissue of that internal cavity, in particular, characteristics such as:

Access—ease of introducing liquid or gel into the cavity

Tissue type that defines adhesiveness—ability to attach reliably and consistently polymer to the cavity tissue

Internal movement—effected by gravitational motion, stretching, peristaltic motion, etc. that cause periodical changes in the shape and volume of the cavity—pressure and volume regime

Wetness—to enable diffusion of drugs into the tissue

Degradability mechanism—flow of liquids or aqueous solutions, e.g. urine, serous or lymphatic fluids,

The specific values of cavity characteristics require careful consideration in the development of topical drugs suitable for treatment of diseases inside these cavities.

Table 1 summarizes the different organs, types of tissue their inner lining is made of and characteristics of the surrounding medium.

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## v. Chemotherapy—Anticancer Drugs

Many chemotherapy (antineoplastic) drugs used as cancer treatments bind to DNA, resulting in synthesis inhibition and strand breakage. In standard intravesical instillations, chemotherapy drugs are administered at dose concentrations of around 1 mg/ml for 1-2 hour sessions.

In the particular case of treatment of bladder cancer, the bladder tissue penetration by chemotherapy drugs—a critical parameter in treatment effectiveness—exhibits a linear relationship with the concentration of the chemotherapy drugs (see Gao X, Au J L, Badalament R A, Wientjes M G. Bladder tissue uptake of mitomycin C during intravesical therapy is linear with drug concentration in urine. Clin Cancer Res. 1998 January; 4(1):139-43)). Furthermore, chemotherapy drug penetration is 40% higher in the tumor tissue than in the adjacent normal urothelium. Gao et al demonstrated double Mitomycin C (MMC) concentration in tissue when installing 40 mg/20 ml as compared with 20 mg/20 ml MMC: human bladder tumors had a significantly higher tissue uptake of MMC than the normal bladder tissue.

The anti-tumor effect of chemotherapy drugs depends on concentration and exposure time. Schmittgen et al (see Schmittgen T D, Wientjes M G, Badalament R A, Au J L.

System	Organ	Type of Tissue	Elasticity Mobility	pH	Surroundings
Digestive	Mouth/Tongue	Mucosal	Very	Neutral	Flow of food and liquids
	Esophagus	Mucosal	None	Neutral	Flow of food and liquids
	Stomach	Mucosal	Very	Strongly acidic	Very acidic fluids, enzymatic activity
	Duodenum	Mucosal	Moderate	Slightly alkaline	Flow of bolus, enzymatic activity
	Small intestine	Mucosa, ciliated	Moderate	Slightly alkaline	Flow of bolus, enzymatic activity, absorption of nutrients
	Large intestine	Mucosal	Moderate	Slightly alkaline	Flow of feces
Respiratory	Rectum	Mucosal	Moderate	Slightly alkaline	Flow of feces
	Mouth/Nose	Mucosal	None	Neutral	Flow of air and humidity
	Larynx	Mucosal	Moderate	Neutral	Flow of air and humidity
	Eustachian tubes	Mucosal, ciliated	None	Neutral	Presence of air, humidity
	Pharynx	Mucosal	Moderate	Neutral	Flow of air and humidity
	Trachea	Mucosal	None	Neutral	Flow of air and humidity
Urinary	Lungs/Alveoli	Mucosal	Moderate	Neutral	Flow of air and humidity
	Kidneys	Mucosal	None	Slightly acidic	Blood filtration, production of urine
	Ureters	Mucosal	None	Slightly acidic	Flow of urine
	Bladder	Mucosal	Very	Slightly acidic	Accumulation and evacuation of urine
	Prostate	Mucosal	None	Slightly acidic	Flow of urine and semen (slightly alkaline in ejaculation)
	Urethra	Mucosal	Moderate	Slightly acidic	Flow of urine and semen (in the males)
Genital	Vas deferens	Mucosal, ciliated	None	Neutral	Flow of seminal fluids
	Epididymis	Mucosal, ciliated	None	Neutral	Flow of seminal fluids
	Testes	Mucosal	Moderate	Neutral	Production of seminal fluids
	Vagina	Mucosal	None	Neutral	Coitus, flow of semen, flow of menstrual fluids
	Cervix	Mucosal	Moderate	Neutral	Flow of semen, flow of menstrual fluids
	Fallopian tubes	Mucosal, ciliated	None	Neutral	Flow of semen, flow of menstrual fluids
Pleura	Ovules	Mucosal	None	Neutral	Production of ova
	Pleural membranes	Serous	Moderate	Neutral	Pleural fluids
Peritoneum	Peritoneal membranes	Serous	Moderate	Neutral	Peritoneal fluids

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Pharmacodynamics of mitomycin C in cultured human bladder tumors. *Cancer Res.* 1991 Aug. 1; 51(15):3849-56) demonstrated, both in TCC cell cultures and human bladder tumor tissue cultures, that a ten times higher concentration was needed in order to get a similar cell kill effect when exposure time to MMC was reduced from 24 hours to two hours.

The proven conclusion is that maintaining higher drug concentration for longer treatment duration will enhance the treatment efficacy.

vi. Required Properties for Topical Treatment in the Bladder and Other Internal Cavities

One approach to treatment of diseases of internal body cavities such as the bladder is topical application of a therapeutic agent entrained in a suitable matrix/mixture. The properties of the materials to be used in such a matrix/mixture must be adapted to the needed medical effect.

Important properties include:

Rheological properties (viscosity, thixotropy,  $G'$ ,  $G''$ )—required for the introduction of the material into the internal cavity

Adhesion—required to coat dependably the target tissue  
Flexibility—to comply with the volume and shape natural changes of the internal cavity under treatment

Dilution in aqueous solution—to enable API release and natural expelling of the material through body fluids  
Mechanical properties, such as hardness, tensile strength to provide

Duration of time that the material remains in the internal cavity before it degrades

A suitable Active Pharmaceutical Ingredient (API)—the medical drug or drug derivative chosen from the families listed in section iii

Loading of drug or API in the material. For certain clinical protocol the amount and concentration of the drug or API mixed into the material have to be set to a prescribed level. The amount of therapeutic agent thus used can be significantly lower than used in regular parallel instillations and more than a single API can be loaded. So the API part of the administered material may vary from zero concentration (gel only) to 50% (e.g., for DMSO).

The ability of the matrix/mixture to release the drug in a controlled manner such that the actual drug concentration vis-à-vis the organ tissue or lining upon which the mixture is adhered will be optimal for each treatment. It is precisely the specific composition of the mixture that determines the release profile of the drug and its adsorption into the target tissue. For example, if the API is lipophilic, the addition of certain surface-active agents in given concentrations will provide for their emulsification, easier release from the drug composition and easier absorption by the internal organ lining.

Drug viability. The material is designed and tested not to reduce the viability duration of the drug or API that is mixed into it, so that the amount that is released throughout the treatment will have the optimal therapeutic effect.

vii. Limitations of Superficial Bladder Cancer (SBC) Treatments Known in the Art

SBC is a highly-recurrent form of cancer. To lower recurrence, it is considered necessary to treat patients with a single intravesical chemotherapy instillation immediately after TUR-T.

A meta-analysis of 7 randomized trials (1,476 patients with a median follow-up of 3.4 years) has demonstrated that one chemotherapy instillation immediately after Tumor

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resection (TUR) decreases the relative risk of recurrence by 40% (see Sylvester R J, Oosterlinck W, van der Meijden A P. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol.* 2004 June; 171(6 Pt 1):2186-90). The timing of the instillation is crucial: in all studies, instillation was administered within 24 hours. A study reported that if the first instillation was not given within 24 hours, the risk of recurrence increased twofold (see Kaasinen E, Rintala E, Hellström P, Viitanen J, Juusela H, Rajala P, Korhonen H, Liukkonen T; FinnBladder Group. Factors explaining recurrence in patients undergoing chemioimmunotherapy regimens for frequently recurring superficial bladder carcinoma. *Eur Urol.* 2002 August; 42(2):167-74).

Following resection and first immediate treatment patients need to be stratified by their risk for tumor progression and recurrence:

Patients with low risk for disease progression/recurrence (30%)—need no further instillations.

Intermediate risk patients (40-50%)—usually receive 6 additional sessions of Mitomycin C (MMC) chemotherapy instillations.

High risk patients (20%)—are treated with 6 intravesical *Bacillus Calmette-Guerin* (BCG) instillations.

The efficacy of the current standard topical chemotherapy treatment for Superficial Bladder Cancer (intravesical instillation) is limited, because there is no control on the chemotherapy concentration and the time until it is expelled. In an attempt to prolong the standard treatment to two hours, some physicians dictate behavioral conditions to reduce acidity of the bladder, to reduce the volume of urine before the instillation and instill maximal concentration of chemotherapy dissolved in minimal volume of saline.

There are several obstacles and complications known that accompany the presently used methods for coating the internal wall of the bladder (and hence for topical treatments for bladder cancer):

The mucosal membrane. One of the physiological purposes of the mucosal membrane that covers the bladder's inner wall, which is permanently soaked in urine (i.e., a watery composition), is to prevent adherence of foreign bodies to it. Therefore, any composition targeted to adhere to the internal wall of the bladder will have to overcome the difficulty of adhering to such mucosal membrane. Furthermore, since the mucosal layer is in constant contact with urine, in order to coat it, a hypothetical option would be to initially dry it. However, such an operation is not acceptable in present medical practice. Another complication stems from the membrane structure, which is composed from several cell layers where the outermost is the terminally differentiated 'umbrella' cells that are the urothelium most superficial layer. Regular biological adhesives, such that are used to stop bleeding (e.g. Tabotamp that is distributed by Johnson & Johnson, NJ, USA), can bond strongly through the wet surface and peel-off that delicate, outermost layer and thus damage the membrane. The achievement of a satisfactory non-damaging coating of wet, non-adherent mucosal tissue is very challenging indeed.

The bladder's natural expansion and collapse. The bladder is essentially muscular tissue and its wall is naturally highly flexible. The inner volume of a mature bladder varies greatly, from a collapsed or 'empty' state with a volume of 0-30 ml up to a filled bladder with a



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volume of up to 500-600 ml (though the bladder usually fills only up to 150-200 ml before micturition point, that is, when the individual feels the urge to urinate and indeed vacates the bladder. Therefore, providing a composition that has the capacity to adhere and conform to the bladder wall without damaging the outer layer, adapt itself to the bladder's morphology in spite of the great variance in volume and the fact that it is permanently changing its form and volume and stay adhered to it is considered an enormous challenge. Further to the above mentioned difficulties to adhere onto a mucosal membrane, it is also highly challenging to do so while avoiding the peeling-off of the outermost layer of the membrane—due to adhering shear forces or adhesion between tissue areas. So while biological glues that can stop bleeding can also adhere through the wet mucosal layer, their rigidity compromises the integrity of the outermost layer and negates the required therapeutic effect.

The same obstacles, to even greater extent, are relevant to the treatment of the same cancer (transitional cell carcinoma) in the upper urinary tract. TCC in the upper urinary tract is a rare urological disease and has a propensity for multifocality, local recurrence, and development of metastases. Almost 5% of all urothelial neoplasms occur in the kidney and ureters. The standard treatment for patients with upper tract TCC and a normal kidney is a complete removal of the involved kidney, ureter and bladder cuff. A less-invasive treatment, namely resection of tumors followed by instillation with chemotherapy or immunotherapy, is recommended for patients with anatomic or functional solitary kidneys, bilateral upper-tract TCC, base line renal insufficiency, or inability to tolerate major surgery. Patients with a normal contralateral kidney who have small, low-grade lesions can also be reasonable candidates for this organ conserving management.

Topical immunotherapy or chemotherapy instillations for treatment of UTUC are used as primary or adjuvant treatment in order to reduce tumor recurrence. Topical instillation is performed using either infusion through a percutaneous nephrostomy tube, via a retrograde ureteral catheter, or by retrograde reflux from the bladder with an indwelling double-J stent. The main disadvantage in all these treatments is the short residual duration of the active agent in the treated area resulting in a low exposure time essential for treatment efficacy. This may be one of the reasons for the shorter average disease-free duration of upper tract TCC patients, compared to lower tract TCC patients.

Another bladder disease is overactive bladder (OAB)—when the bladder contracts suddenly without patient's control when the bladder is not full. This syndrome affects an estimated 1 in 11 adults in the United States—especially common in older adults.

Current available treatment options for OAB are: bladder training, pelvic floor exercises, drug therapy such as anti-cholinergics, capsaicin, intravesical botulinum toxin injections and in severe cases—bladder augmentation surgery.

Current oral drugs have high adverse event rate which leads to patients' intolerance. Bladder instillation with antimuscarinics has been tried with lower adverse event rate, but require recurrent catheterization due to the drug relatively short half-life that reduces compliance.

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Despite promising results the drawbacks to intravesical botulinum toxin injections are numerous: the cystoscopic injection requires proficiency and authorization of the physician, some degree of anesthetic administration is required, the botulinum toxin effects only the injected anatomical locations and the treatment may lead to temporary urinary retention and need for self-catheterization.

#### viii. Mechanical Support and Sustained Drug Release in Minimally-Invasive Surgery

The limited number of access ports used in laparoscopic surgery may impair the ability of the surgeon to achieve adequate retraction and exposure, or to stabilize “moving targets” while operating on nonfixed organs. Current solutions include adding more ports or using a hand-assisted technique—which have the disadvantages of being more invasive, possibly creating a cumbersome situation of multiple instruments in a limited working space—or the use of temporary sutures that pass through the abdominal wall.

The current invention provides means by which the organs can be held mechanically in place by injecting the invented materials into the cavity and letting them to solidify and support the internal organs. This invented materials and method have the additional advantages of a) serving as a soothing dressing for the surgery cuts, b) contribution to healing through sustained release of anti-infection drug and analgesic drug for a therapeutically-significant duration (e.g., over 6 hours), and c) avoiding the need for further surgical or medical procedure, by natural degradation of the material and its expelling from the body.

Similar method, but with a different family of materials can be used to prevent the adhesion of tissues between organs in the treated area, which may often occur during laparoscopic surgery.

#### ix. Current State-of-the-Art

To the best of the inventors' knowledge, a method for treating diseases of the bladder or other inner cavities based on production of a solidified coating layer and affixing it onto the internal wall of the bladder or other cavities, followed by continuous release of the therapeutic agent(s) from the coating, remains unknown in the art.

Furthermore, the application of the substrate material such that it creates a continuous layer substantially affixed to the mucosal lining of the bladder or the outermost tissue of other internal cavity for prolonging the exposure of the drug to the targeted cells is neither trivial nor obvious to any person skilled in the art.

Compositions known in the prior art as sustained-release substrates for the treatment of bladder cancer (for example, the invention disclosed in U.S. Pat. Appl. US2006/0127420 to Chung) are lipophilic (oil-based). Given that the inner bladder wall is mucosal, essentially and permanently soaked in an aqueous medium (i.e., urine), a drug embedded in a hydrophilic medium would more effectively diffuse through the matrix/mixture and conveniently reach the bladder wall, allowing in that way an intimate, continuous contact between the drug and the bladder wall.

Thus, there remains a long-felt and unmet need for a material with the following properties: it is hydrophilic; it provides a homogeneous layer that can securely adhere to the surfaces of internal body cavities, in particular, mucosal tissue of such cavities as the bladder; it remains attached despite the natural motions of the tissue to which it is attached; it is easily applied; it is biocompatible; it provides a continuous sustained release of a therapeutic agent; the rate of release of the therapeutic agent is determined by the concentration of the agent and the rate of degradation of the

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material; and after the material degrades, it is excreted from the body by the body's own natural processes.

#### SUMMARY OF THE INVENTION

The current invention is designed to answer this long-felt need. It comprises a series of systems that combine therapeutic materials and application means for the topical treatment of diseases that are focused in internal cavities, such as a system for treating Superficial Bladder Cancer (SBC).

It is therefore an object of the present invention to disclose the use of a thermoreversible hydrogel composition in a system for delivery of a therapeutic agent to the urinary tract, characterized in that said thermoreversible hydrogel composition comprises a thermoreversible hydrogel characterized by: a viscosity of less than 200 Pa·s over a temperature range of 4° C.-12° C.; a viscosity of greater than 103 Pa·s at 37° C.; a "peel strength" adhesiveness according to ASTM standard D2256-03 of 0.5-5.0 N cm-2 at 37° C.; and, flexibility sufficient such that a 3 cm2×3 cm2 section of bladder tissue layered with said thermoreversible hydrogel at room temperature can be stretched to 9 cm2×9 cm2 without detachment of said thermoreversible hydrogel from said bladder tissue.

It is a further object of this invention to disclose such a use of a thermoreversible hydrogel composition in a system for delivery of a therapeutic agent to the urinary tract, wherein said composition additionally comprises an effective amount of at least one therapeutic agent for treatment of the urinary tract.

It is a further object of this invention to disclose the use of a hydrogel composition in a system for delivery of a therapeutic agent to the pleura, characterized in that said hydrogel composition comprises a thermoreversible hydrogel characterized by a viscosity of less than 5 Pa·s over a temperature range of 4° C.-12° C.; a viscosity of greater than 103 Pa·s at 37° C.; a "peel strength" adhesiveness according to ASTM standard D2256-03 of 0.5-5.0 N cm-2 at 37° C.; and flexibility sufficient such that a 3 cm2×3 cm2 section of bladder tissue layered with said thermoreversible hydrogel at room temperature can be stretched to 9 cm2×9 cm2 without detachment of said thermoreversible hydrogel from said bladder tissue.

It is a further object of this invention to disclose the use of a hydrogel composition in a system for delivery of a therapeutic agent to the pleura, wherein said composition additionally comprises an effective amount of a therapeutic agent for treatment of the pleura.

It is a further object of this invention to disclose the use of a thermoreversible hydrogel composition in a system for delivery of a therapeutic agent to a mucosal or serous membrane, characterized in that said hydrogel composition comprises a thermoreversible hydrogel characterized by a viscosity of less than 5 Pa·s over a temperature range of 4° C.-12° C.; a viscosity of greater than 103 Pa·s at 37° C.; a "peel strength" adhesiveness according to ASTM standard D2256-03 of 0.5-5.0 N cm-2 at 37° C.; and flexibility sufficient such that a 3 cm2×3 cm2 section of bladder tissue layered with said thermoreversible hydrogel at room temperature can be stretched to 9 cm2×9 cm2 without detachment of said thermoreversible hydrogel from said bladder tissue.

It is a further object of this invention to disclose such a use of a thermoreversible hydrogel composition in a system for delivery of a therapeutic agent to a mucosal or serous membrane, wherein said composition additionally com-

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prises an effective amount of a therapeutic agent for treatment of a mucosal or serous membrane.

It is a further object of this invention to disclose such a use of a thermoreversible hydrogel composition in a system for delivery of a therapeutic agent to a mucosal or serous membrane, wherein said mucosal or serous membrane is located at an internal cavity chosen from the group consisting of, mouth, nasal sinus, paranasal sinus, gallbladder, esophagus, rectum, lungs, vagina, uterus, stomach, renal pelvis, pleura, abdomen, peritoneum, pelvis, liver, kidney, heart, intestine, brain, and vertebral column.

In some embodiments of the invention, said thermoreversible hydrogel is further characterized by a viscosity of less than 5 Pa·s over a temperature range of 4° C.-12° C. In some embodiments of the invention, the said thermoreversible hydrogel is further characterized by a viscosity of less than 0.5 Pa·s over a temperature range of 4° C.-12° C. In some embodiments of the invention, the thermoreversible hydrogel is further characterized by a viscosity of greater than 3×103 at 37° C.

In some embodiments of the invention, said thermoreversible hydrogel has a "peel strength" adhesiveness according to ASTM standard D2256-03 of 1.0-5.0 N cm-2 at 37° C.

In some embodiments of the invention, said thermoreversible hydrogel is additionally characterized by flexibility sufficient to permit the volume of the tissue to which said composition is applied to expand by a factor of at least 3 without detachment of said gel from said tissue.

In some embodiments of the invention, said thermoreversible hydrogel comprises between 20% and 30% (w/w) ethylene oxide/propylene oxide block copolymer; between 0.05% and 0.5% (w/w) hydroxypropylmethylcellulose (HPMC); between 0.1% and 2.5% (w/w) polyethylene glycol (PEG)-400; and the balance water.

In some embodiments of the invention, said thermoreversible hydrogel comprises between 20% and 30% (w/w) ethylene oxide/propylene oxide block copolymer; between 0.1% and 0.3% (w/w) HPMC; between 0.1% and 1.8% (w/w) PEG-400; and the balance water.

In some embodiments of the invention, said thermoreversible hydrogel comprises between 18% and 40% (w/w) ethylene oxide/propylene oxide block copolymer; between 0.05% and 0.8% (w/w) CMC; between 0.1% and 2.5% (w/w) PEG-400; and the balance water.

In some embodiments of the invention, said thermoreversible hydrogel comprises between 12-30% Pluronic F127; between 5-30% Pluronic F68; between 0.05% and 2% (w/w) CMC; between 0.1% and 2.5% (w/w) PEG-400; and the balance water.

It is a further object of this invention to disclose such a use as defined in any of the above, wherein said thermoreversible hydrogel additionally comprises at least one component selected from the group consisting of adhesive and thickening compounds; bonding agents; pH-modifying substances; diffusion coatings; plasticizers; components for increasing permeability within the formulation; swellable excipients; matrix forming polymers; tight junction modifiers/cell membrane permeability enhancers; and any combination thereof.

In some embodiments of the invention, said bonding agent is selected from the group consisting of polycarophil, cellulose, microcrystalline cellulose, cellulose derivatives, HPMC, hydroxypropylcellulose (HPC), low-substituted hydroxypropylcellulose, dicalcium phosphate, lactose, sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), polyvinylpyrrolidone (PVP),

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vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides, hyaluronic acid, fats, fatty acid derivatives, and any combination thereof.

In some embodiments of the invention, said diffusion coating is chosen from the group consisting of ethylcelluloses and polymethacrylates, cellulose acetate and cellulose acetate butyrate or any combination thereof.

In some embodiments of the invention, said component for increasing permeability within the formulation is chosen from the group consisting of polyethylene glycols, PVP, PVA, HPMC, HPC, hydroxyethylcelluloses (HEC), methylcellulose (MC), carboxymethylcelluloses and their salts, dextrins, maltodextrins, cyclodextrins, dextrans, urea, salts, sugars, sugar alcohols, and any combination thereof.

In some embodiments of the invention, said swellable excipient is selected from the group consisting of polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl starch, polyethylene oxides, polymethacrylates, L-HPC, cellulose acetate, ethylcellulose, polymethacrylates, high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, poly(hydroxyalkyl methacrylate), alginates, galactomannans, and any combination thereof.

In some embodiments of the invention, said matrix forming polymer is selected from the group consisting of hydroxyethylmethylcelluloses, HPC, HEC, MC, ethylcelluloses, alkylcelluloses, hydroxyalkylcelluloses, hydroxyalkylmethylcelluloses, sodium CMCs, alginates, galactomannans, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives, polyvinyl alcohols, partially hydrolysed polyvinyl acetate, polyvinylpyrrolidone, agar, pectin, gum arabic, tragacanth, gelatin, starch, starch derivatives poly(propylene oxide) (PPO), poly(lactide-co-glycolic acid) (PLGA), poly(N-isopropylacrylamide) (PNIPAM), poly(propylene fumarate) (PPF), polyurethane (PU), poly(organophosphazene) (POP), stearic acid, poly(acrylic acid), glyceryl stearate, cetearyl alcohol, sodium stearyl lactylate, hydroxy-lanolin, and any combination thereof.

In some embodiments of the invention, said tight junction modifier/cell membrane permeability enhancer is chosen from the group consisting of anionic surfactants, non-anionic surfactants, charged polymers, dimethyl sulfoxide (DMSO), decylmethyl sulfoxide, tert-butyl cyclohexanol, fatty acids their esters and salts, ethanol, nicotinamide, urea, perfluoropolyether, monoterpene ketones, disodium citrate, succinic acid and tris.

In some embodiments of the invention, said surfactant is chosen from the group consisting of polysorbates, sodium dodecyl sulfate, and dextran sulfate.

In some embodiments of the invention, said charged polymer is chosen from the group consisting of chitosan poly-arginine, polylysine, and alginate.

In some embodiments of the invention, said monoterpene ketone is chosen from the group consisting of like (-) menthol, (-) menthone, peppermint oil, and spearmint oil.

In some embodiments of the invention, said thermoreversible hydrogel is additionally used as a biological glue.

It is a further object of this invention to disclose such a use as defined in any of the above, further characterized in that said composition releases said therapeutic agent, over a

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temperature range of 36° C.-42° C. and a pH range of between 5.5 and 8.0, at a rate of 80% in a time range of between 3 and 30 hours.

It is a further object of this invention to disclose such a use as defined in any of the above, further characterized in that said composition releases said therapeutic agent, over a temperature range of 36° C.-42° C. and a pH range of between 1 and 9.0, at a rate of 80% in a time range of between 3 and 30 hours.

It is a further object of this invention to disclose such a use as defined in any of the above, further characterized in that said composition releases said therapeutic agent, over a temperature range of 36° C.-42° C. and a pH range of between 1 and 9.0, at a rate of 80% in a time range of between 2 and 4 weeks.

It is a further object of this invention to disclose such a use as defined in any of the above, wherein said therapeutic agent for treatment of the urinary tract is selected from the group consisting of antineoplastic agents, chemotherapeutic agents, anti-infective agents, antimicrobial agents, antiparasitic agents, antiviral agents, agents acting on the blood, antihemorrhagics, antithrombotic agents, antifungals, antiseptics, agents for treating diseases of the genito-urinary system, anti-inflammatory agents, neurological agents, gene therapy agents, corticosteroids, analgesic and anesthetic agents, growth factors, VEGF, inhibitory factors, LIF, proteins, mucin, and any combination thereof.

It is a further object of this invention to disclose such a use as defined in any of the above, wherein said therapeutic agent for treatment of the urinary tract is selected from the group consisting of Mitomycin C, Doxorubicin, Valrubicin, and Gemcitabine, Thiotepa, Ethoglucid (Epodyl), Epirubicin, Pirarubicin, Apaziquone, Vicinium and botulinum toxin, and interleukin-2.

It is a further object of this invention to disclose such a use as defined in any of the above, wherein said system further comprises a second hydrogel composition used subsequently, said second hydrogel composition comprising a thermoreversible hydrogel characterized by a viscosity of less than 200 Pa·s over a temperature range of 4° C.-12° C.; a viscosity of greater than 103 Pa·s at 37° C.; a "peel strength" adhesiveness according to ASTM standard D2256-03 of 0.5-5.0 N cm<sup>-2</sup> at 37° C.; and flexibility sufficient such that a 3 cm<sup>2</sup>×3 cm<sup>2</sup> section of bladder tissue layered with said thermoreversible hydrogel at room temperature can be stretched to 9 cm<sup>2</sup>×9 cm<sup>2</sup> without detachment of said thermoreversible hydrogel from said bladder tissue; and an effective amount of a cell cycle modifying agent for synchronization of cell cycle chosen from the group consisting of chalones, colcemid, methotrexate, and thymidine.

It is a further object of this invention to disclose such a use as defined in any of the above, wherein said system is further characterized in that it is designed to release said therapeutic agent continuously for at least 12 hours.

It is a further object of this invention to disclose a method for administering a therapeutic agent to the internal surface of an internal body cavity, comprising:

incorporating an effective amount of said therapeutic agent into a biocompatible sustained-release material chosen from the group consisting of (a) biocompatible sustained-release materials comprising between 20% and 30% (w/w) ethylene oxide/propylene oxide block copolymer, between 0.05% and 0.5% (w/w) HPMC, between 0.1% and 2.5% (w/w) PEG-400, and the balance water; and (b) biocompatible sustained-release materials comprising between 20% and 30% (w/w) ethylene oxide/propylene oxide block copolymer;



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between 0.1% and 0.3% (w/w) HPMC; between 0.1% and 1.8% (w/w) PEG-400; and the balance water; inflating a balloon to open said internal body cavity to a substantially symmetrical shape; introducing said biocompatible sustained-release material into said internal body cavity; applying said biocompatible sustained-release material to at least part of the internal surface of said internal body cavity; applying force to said material, thereby spreading it over at least part of the internal surface of said internal body cavity; causing said biocompatible sustained-release material to adhere to said internal surface of said internal body cavity; and, releasing said therapeutic agent into said internal body cavity under conditions chosen from the group consisting of:

a temperature of 36-42° C.; pH in the range of 5.5-8.0, and at a rate of 80% in a time range of 3 to 30 hours; a temperature of 36-42° C.; pH in the range of 1-9.0, and at a rate of 80% in a time range of 3 to 30 hours; and, a temperature of 36-42° C.; pH in the range of 1-9.0, and at a rate of 80% in a time range of 2 to 4 weeks.

is a further object of this invention to disclose such a method, additionally comprising a step of providing said material with at least one component selected from the group consisting of adhesive and thickening compounds; at least one substance selected from the group consisting of polycarbophil, cellulose, microcrystalline cellulose, cellulose derivatives, dicalcium phosphate, lactose, PVP and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides, fats and fatty acid derivatives and any combination thereof; pH-modifying substances; at least one substance selected from the group consisting of ethylcelluloses and polymethacrylates, cellulose acetate, cellulose acetate butyrate and any combination thereof; plasticizers; at least one substance selected from the group consisting of polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl starch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC), cellulose acetate, ethylcellulose and polymethacrylates, high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, cross-linked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl starch, poly(hydroxyalkyl methacrylate), alginates, galactomannans, and any combination thereof; at least one substance chosen from the group consisting of polyethylene glycols, PVP, PVA, HPC, hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans urea, salts, sodium chloride, potassium chloride, ammonium chloride, sugars, sucrose, lactose, glucose, fructose, maltose, sugar alcohols, mannitol, sorbitol, xylitol, lactitol, and any combination thereof; at least one substance chosen from the group consisting of hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, alkylcelluloses, hydroxyalkylcelluloses hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives,

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polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch, starch derivatives and any combination thereof; and any combination thereof.

It is a further object of this invention to disclose such a method, wherein said step of releasing said therapeutic material into said internal body cavity further comprises a step of dissolving said biocompatible sustained-release material in body fluid found within said internal body cavity, whereby said therapeutic agent is released from said biocompatible sustained-release material.

It is a further object of this invention to disclose such a method, wherein said step of applying force to said material further comprises a step of filling said catheter balloon with a liquid and positioning the patient to utilize the gravitational forces directly toward the target tissue during the solidification of the material and cause optimal adhesion to that target tissue.

It is a further object of this invention to disclose such a method, wherein said step of applying force to said material further comprises a step of changing the position of the patient before applying partial doses of material to enable substantially full coating of the whole targeted internal cavity surface.

It is a further object of this invention to disclose such a method, wherein said step of applying force to said material further comprises inserting a magnetic material chosen from the group consisting of a magnet, a magnetic metal, and a ferromagnetic liquid into said balloon; and applying an external magnetic field such that the interaction said magnetic material and said external magnetic field causes said magnetic material to move within said balloon, thereby applying force to at least part of the internal surface of said internal cavity.

It is therefore an object of the present invention to disclose a hydrophilic biocompatible sustained-release material comprising Pluronic F-127 and Hydroxypropylmethylcellulose (HPMC) in amounts effective to produce a hydrogel composition of sufficiently low viscosity at room temperature to be injectable into an internal body cavity via a tube inserted within a urinary catheter, trocar or the working channel of an endoscope.

It is a further object of this invention to disclose such a material, further comprising PEG-400 or PEG-800.

It is a further object of this invention to disclose such a material as defined in any of the above, additionally comprising at least one active ingredient (API).

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said API comprises excipients selected from acids or buffer substances adapted to modify the pH so as to reduce the dependence of said release of active ingredient on the pH of the release medium.

It is a further object of this invention to disclose such a material as defined in any of the above, additionally comprising at least one more compounds selected from adhesive and thickening compounds; bonding agents; pH-modifying substances; diffusion coating; plasticizers; matrix permeability increasing components; swellable excipients matrix-forming polymers; diffusion-controlled or pulsatile formulations; reverse thermal gelation agents or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said adhesive and thickening compounds are selected from a group consisting of polycarbophil, acrylic acid crosslinked, divinyl glycol, hydroxypropylmethylcellulose (HPMC),



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polyvinylpyrrolidone (PVP), methylcellulose (MC), hydroxy-propylcellulose (HPC), other hydroxyalkylcelluloses, hydroxyalkylmethylcelluloses, carboxy-methylcelluloses and salts thereof, polyacrylic acids, polymethacrylates, gelatin, starch or starch derivatives, as well as gums like guar gum and xanthan gum or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said bonding agents are selected from a group consisting of polycarbophil, cellulose, microcrystalline cellulose, cellulose derivatives such as, for example, HMPC, HPC and low-substituted hydroxypropylcellulose (L-HPC), dicalcium phosphate, lactose, PVP and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPM-CAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides (e.g. alginic acid, alginates, galactomannans) waxes, fats and fatty acid derivatives or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said pH-modifying substances are selected from a group consisting of acids, bases and buffer, adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, toluenesulphonic acid, trometamol, tartaric acid. Citric acid, succinic acid, tartaric acid, potassium hydrogen tartrate are preferably employed or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said diffusion coating are selected from a group consisting of ethylcelluloses and polymethacrylates such as, for example, EUDRAGIT® NE, EUDRAGIT® RS and RL, cellulose acetate and cellulose acetate butyrate or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said plasticizers are selected from a group consisting of citric acid derivatives, triethyl citrate, tributyl citrate, acetyl triethyl citrate, phthalic acid derivatives, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, benzoic acid and benzoic esters, other aromatic carboxylic esters, trimellithic esters, aliphatic dicarboxylic esters, dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters, glycerol monoacetate, glycerol diacetate or glycerol triacetate, polyols, glycerol, 1,2-propanediol, polyethylene glycol of varying chain length, fatty acids and derivatives, glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol, fatty acid alcohols, cetyl alcohol, cetylstearyl alcohol or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein the proportion of the plasticizer is from 0 to 50%, preferably 0 to 35% of the hydrogel composition.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said water-soluble polymers are selected from a group consisting of polymers polyethylene glycols, PVP, PVA, HPMC, HPC, hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans urea, salts, sodium chloride, potassium chloride, ammonium chloride, sugars, sucrose, lactose, glucose, fruc-

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tose, maltose, sugar alcohols, mannitol, sorbitol, xylitol, lactitol, or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said swellable excipients are selected from a group consisting of polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl starch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC), cellulose acetate, ethylcellulose and polymethacrylates, high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl starch, poly(hydroxy-alkyl methacrylate), alginates and galactomannans and mixtures thereof or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said reverse thermal gelation compositions are selected from a group consisting of Poloxamers, Poloxamer 407 or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said water-swallowable matrix-forming polymers compositions are selected from a group consisting of hydroxy-propylmethylcelluloses (HPMC), hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, alkylcelluloses, hydroxy-alkylcelluloses hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans such as, for example, guar and carob flour, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch or starch derivatives or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is formulated as a homogeneous mixture.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is administered orally, topically, intranasal, vaginally, rectal, ocular and parenteral routes.

It is a further object of this invention to disclose such a material as defined in any of the above, further comprising lidocaine.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is soluble in at least one body fluid chosen from the group consisting of urine, serous fluids, and lymphatic fluids.

It is a further object of this invention to disclose such a material, wherein the solubility of said material is sufficiently high that said material will completely degrade in less than 4 weeks after incorporation into an internal body cavity.

It is a further object of this invention to disclose such a material, wherein the solubility of said material is sufficiently high that said material will completely degrade in less than 24 hours after incorporation into an internal body cavity.

It is a further object of this invention to disclose such a material, wherein the solubility of said material is sufficiently high that said material will completely degrade in less than 18 hours after incorporation into an internal body cavity.

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It is a further object of this invention to disclose such a material, wherein the solubility of said material is sufficiently high that said material will completely degrade in less than 16 hours after incorporation into an internal body cavity.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is adapted to exhibit reverse thermal gelling properties.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is characterized by a viscosity of less than 200 Pa·s at a range of 8° C. to 25° C. and greater than 3000 Pa·s at a range of 35° C.-37° C.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is characterized by a viscosity of less than 200 Pa·s at 10° C. and greater than 3000 Pa·s at 37° C. It is a further object of this invention to disclose such a material, wherein said material is characterized by a viscosity of less than 200 Pa·s at 10° C. and greater than 3500 Pa·s at 37° C.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein the instillation temperature of said material is between 20° C. and 42° C.

It is a further object of this invention to disclose such a material, wherein said material is characterized by a gel point below 20° C.

It is a further object of this invention to disclose such a material as defined in any of the above, adapted to adhere to the surface of mucosal tissue.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is characterized by a "rolling ball" adhesiveness according to the ASTM D-3121-94 standard is less than 2 cm.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is characterized by a "peel strength" adhesiveness according to the ASTM D-2256-03 standard is at least 1N/cm<sup>2</sup>.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is characterized by a work of adhesion of at least 0.5 mJ.

It is a further object of this invention to disclose such a material, wherein said material is characterized by a work of adhesion of at least 0.7 mJ.

It is a further object of this invention to disclose such a material, wherein said material is characterized by a work of adhesion of at least 1 mJ.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is characterized by a peak detachment force of at least 1.3 N.

It is a further object of this invention to disclose such a material, wherein said material is characterized by a peak detachment force of at least 14.4 N.

It is a further object of this invention to disclose such a material, wherein said material is characterized by a peak detachment force of at least 6.3 N.

It is a further object of this invention to disclose such a material, wherein said mucosal tissue comprises interior wall of at least one selected from a group consisting of the urinary bladder, mouth, nasal and paranasal sinus, gallbladder, esophagus, rectum, lungs, vagina, uterus, stomach, renal

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pelvis, pleura, abdomen, peritoneum, pelvis, liver, kidney, heart, intestine, brain, vertebral column, or any combination thereof.

It is a further object of this invention to disclose such a material, adapted to remain adherent to said mucosal tissue during the natural expansion on contraction of said urinary bladder or other organs.

It is a further object of this invention to disclose such a material as defined in any of the above, further comprising an effective amount of a therapeutic agent.

It is a further object of this invention to disclose such a material, comprising 20-30% Pluronic F-127; 0-1.8% PEG-400; 0.1%-0.3% HPMC; an effective amount of a therapeutic agent; and the balance water.

It is a further object of this invention to disclose such a material, comprising 20-30% Pluronic F-127; 0-2.5% PEG-400; 0.05%-0.5% HPMC; an effective amount of a therapeutic agent; and the balance water.

It is a further object of this invention to disclose such a material, wherein said therapeutic agent is chosen from the group consisting of Mitomycin C, Doxorubicin (with or without antibiotics), Valrubicin, and Gemcitabine, Thiotepe, Ethoglucid (Epodyl), Epirubicin, Pirarubicin, Apaziquone and Vicinium.

It is a further object of this invention to disclose such a material, wherein said therapeutic agent is mitomycin C.

It is a further object of this invention to disclose such a material, wherein said mitomycin C is present in a concentration of 0.05%-0.2%.

It is a further object of this invention to disclose such a material, wherein said mitomycin C is present in a concentration of 0.025%-0.3%.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein the solubility of said material is sufficiently low that said therapeutic agent is continuously released for at least 12 hours.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein the solubility of said material is sufficiently low that said therapeutic agent is continuously released for at least 2 hours.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein the solubility of said material is sufficiently low that said therapeutic agent is continuously released for at least 16 hours.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein the solubility of said material is sufficiently low that said therapeutic agent is continuously released for at least 18 hours.

It is a further object of this invention to disclose the use of the material as defined in any of the above in a sustained-release topical treatment of a condition affecting an internal body cavity.

It is a further object of this invention to disclose the use of the material as defined in any of the above in a sustained-release topical treatment for at least one selected from a group of internal cavities that includes, among others, the urinary bladder, mouth, nasal and paranasal sinus, gallbladder, esophagus, rectum, lungs, vagina, uterus, stomach, renal pelvis, pleura, abdomen, peritoneum, pelvis, liver, kidney, heart, intestine, brain, vertebral column, etc.

It is a further object of this invention to disclose such a material as defined in any of the above, additionally comprising at least one active ingredient (API).

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material comprises excipients selected from acids or buffer

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substances adapted to modify the pH so as to reduce the dependence of said release of active ingredient on the pH of the release medium.

It is a further object of this invention to disclose such a material as defined in any of the above, additionally comprising at least one more compounds selected from adhesive and thickening compounds; bonding agents; pH-modifying substances; diffusion coating; plasticizers; matrix permeability increasing components; swellable excipients matrix-forming polymers; diffusion-controlled or pulsatile formulations; reverse thermal gelation agents or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said adhesive and thickening compounds are selected from a group consisting of polycarboxylic acid crosslinked, divinyl glycol, hydroxypropylmethylcellulose (HPMC), polyvinylpyrrolidone (PVP), methylcellulose (MC), hydroxy-propylcellulose (HPC), other hydroxyalkylcelluloses, hydroxyalkylmethylcelluloses, carboxy-methylcelluloses and salts thereof, polyacrylic acids, polymethacrylates, gelatin, starch or starch derivatives, as well as gums like guar gum and xanthan gum or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said bonding agents are selected from a group consisting of polycarboxylic acid, cellulose, microcrystalline cellulose, cellulose derivatives such as, for example, HPMC, HPC and low-substituted hydroxypropylcellulose (L-HPC), dicalcium phosphate, lactose, PVP and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides (e.g. alginic acid, alginates, galactomannans) waxes, fats and fatty acid derivatives or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said pH-modifying substances are selected from a group consisting of acids, bases and buffer, adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, toluenesulphonic acid, trometamol, tartaric acid. Citric acid, succinic acid, tartaric acid, potassium hydrogen tartrate are preferably employed or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said diffusion coating are selected from a group consisting of ethylcelluloses and polymethacrylates such as, for example, EUDRAGIT® NE, EUDRAGIT® RS and RL, cellulose acetate and cellulose acetate butyrate or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said plasticizers are selected from a group consisting of citric acid derivatives, triethyl citrate, tributyl citrate, acetyl triethyl citrate, phthalic acid derivatives, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, benzoic acid and benzoic esters, other aromatic carboxylic esters, trimellitic esters, aliphatic dicarboxylic esters, dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters, glycerol monoacetate, glycerol diacetate or glycerol triacetate, polyols, glycerol, 1,2-propanediol, polyethylene glycol of vary-

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ing chain length, fatty acids and derivatives, glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol, fatty acid alcohols, cetyl alcohol, cetylstearyl alcohol or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein the proportion of the plasticizer is from 0 to 50%, preferably 0 to 35% of the hydrogel composition.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said water-soluble polymers are selected from a group consisting of polymerspolyethylene glycols, PVP, PVA, HPMC, HPC, hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans urea, salts, sodium chloride, potassium chloride, ammonium chloride, sugars, sucrose, lactose, glucose, fructose, maltose, sugar alcohols, mannitol, sorbitol, xylitol, lactitol, or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said swellable excipients are selected from a group consisting of polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl starch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC), cellulose acetate, ethylcellulose and polymethacrylates, high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethylstarch, poly(hydroxyalkyl methacrylate), alginates and galactomannans and mixtures thereof or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said reverse thermal gelation compositions are selected from a group consisting of Poloxamers, Poloxamer 407 or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said water-swellable matrix-forming polymers compositions are selected from a group consisting of hydroxy-propylmethylcelluloses (HPMC), hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, alkylcelluloses, hydroxy-alkylcelluloses hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans such as, for example, guar and carob flour, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch or starch derivatives or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is administered orally, topically, intranasal, vaginally, rectal, ocular and parenteral routes.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said API is released at temperature of 36-42° C.; pH in the range of 5.5-8.0, at a rate of 80% in a time range of 3 to 30 hours.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said API is released at temperature of 36-42° C.; pH in the range of 1-8.0, at a rate of 80% in a time range of 2 hours to 4 weeks.



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It is a further object of this invention to disclose such a material as defined in any of the above, wherein said API is dissolved, suspended and/or solid, amorphous or crystalline form.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said API is provided in various particle sizes, in unground, ground or in micronized form.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material is administered topically; further wherein said API is selected from a group consisting of Antineoplastic drugs; Chemotherapeutic agents; Anti-infective agents, Antimicrobial drugs, Antiparasitic agents, Antivirals; Antihemorrhagics, Antithrombotic agents, antianemic drugs, Dermatologic drugs, antifungals, antiseptic, Genito-urinary system drugs, Gastrointestinal system, antiobesity, acid related disorders, Metabolism drugs, Anti-inflammatory product, Musculoskeletal system acting drugs; Respiratory drugs, Otological drugs, Anti-infective drugs, Corticosteroids drugs, Analgesics drugs, GeneTherapy, Antiparasitics drugs, Growth factors, VEGF, Inhibitory factors, LIF or any combination thereof.

It is a further object of this invention to disclose such a material as defined in any of the above, wherein said material further comprising at least one selected from a group consisting of Poly (propylene oxide)—PPO, Poly (lactide-co-glycolic acid)—PLGA, Poly (N-isopropylacrylamide)—PNIPAM, Poly (propylene fumarate)—PPF, Poly (urethane)—PU, Poly (organophosphazene)—POP, Poloxamers of the type PEO-PPO-PEO (Poly (ethylene oxide), Poly (propylene oxide), Poly (ethylene oxide)) such as poloxamer 68, 88, 98, 108, 124, 127, 188, 237, 338 and 407, Stearic Acid, Poly (acrylic acid), Glyceryl Stearate, Cetearyl Alcohol, Sodium Stearoyl Lactylate, Hydroxy-Lenolin or any combination thereof.

It is a further object of this invention to disclose such a material, wherein said material is used as biological glue.

It is a further object of this invention to disclose a method for administering a therapeutic agent to the internal surface of an internal body cavity, comprising:

- incorporating an effective amount of said therapeutic agent into a biocompatible sustained-release material;
- inflating a balloon to open said internal body cavity to a substantially symmetrical shape;
- introducing said biocompatible sustained-release material into said internal body cavity;
- applying said biocompatible sustained-release material to at least part of the internal surface of said internal body cavity;
- applying force to said material, thereby spreading it over at least part of the internal surface of said internal cavity;
- causing said biocompatible sustained-release material to adhere to said internal surface of said internal body cavity; and,
- releasing said therapeutic agent into said internal body cavity.

It is a further object of this invention to disclose such a method as defined in any of the above, additionally comprising step of providing said material with at least one active ingredient (API).

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said material comprises excipients selected from acids or buffer sub-

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stances adapted to modify the pH so as to reduce the dependence of said release of active ingredient on the pH of the release medium.

It is a further object of this invention to disclose such a method as defined in any of the above, additionally comprising step of providing said material with at least one more compounds selected from adhesive and thickening compounds; bonding agents; pH-modifying substances; diffusion coating; plasticizers; matrix permeability increasing components; swellable excipients matrix-forming polymers; diffusion-controlled or pulsatile formulations; reverse thermal gelation agents or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said adhesive and thickening compounds are selected from a group consisting of polycarbophil, acrylic acid crosslinked, divinyl glycol, hydroxypropylmethylcellulose (HPMC), polyvinylpyrrolidone (PVP), methylcellulose (MC), hydroxypropylcellulose (HPC), other hydroxyalkylcelluloses, hydroxyalkylmethylcelluloses, carboxy-methylcelluloses and salts thereof, polyacrylic acids, polymethacrylates, gelatin, starch or starch derivatives, as well as gums like guar gum and xanthan gum or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said bonding agents are selected from a group consisting of polycarbophil, cellulose, microcrystalline cellulose, cellulose derivatives such as, for example, HMPC, HPC and low-substituted hydroxypropylcellulose (L-HPC), dicalcium phosphate, lactose, PVP and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides (e.g. alginic acid, alginates, galactomannans) waxes, fats and fatty acid derivatives or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said pH-modifying substances are selected from a group consisting of acids, bases and buffer, adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, toluenesulphonic acid, trometamol, tartaric acid. Citric acid, succinic acid, tartaric acid, potassium hydrogen tartrate are preferably employed or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said diffusion coating are selected from a group consisting of ethylcelluloses and polymethacrylates such as, for example, EUDRAGIT® NE, EUDRAGIT® RS and RL, cellulose acetate and cellulose acetate butyrate or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said plasticizers are selected from a group consisting of citric acid derivatives, triethyl citrate, tributyl citrate, acetyl triethyl citrate, phthalic acid derivatives, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, benzoic acid and benzoic esters, other aromatic carboxylic esters, trimellithic esters, aliphatic dicarboxylic esters, dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters, glycerol monoacetate, glycerol diacetate or glycerol triacetate, polyols, glycerol, 1,2-propanediol, polyethylene glycol of varying chain



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length, fatty acids and derivatives, glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol, fatty acid alcohols, cetyl alcohol, cetylstearyl alcohol or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein the proportion of the plasticizer is from 0 to 50%, preferably 0 to 35% of the hydrogel composition.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said water-soluble polymers are selected from a group consisting of polymers polyethylene glycols, PVP, PVA, HPMC, HPC, hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans urea, salts, sodium chloride, potassium chloride, ammonium chloride, sugars, sucrose, lactose, glucose, fructose, maltose, sugar alcohols, mannitol, sorbitol, xylitol, lactitol, or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said swellable excipients are selected from a group consisting of polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl starch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC), cellulose acetate, ethylcellulose and polymethacrylates, high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl starch, poly(hydroxy-alkyl methacrylate), alginates and galactomannans and mixtures thereof or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said reverse thermal gelatin compositions are selected from a group consisting of Poloxamers, in particular Poloxamer 407 or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said water-swelling matrix-forming polymers compositions are selected from a group consisting of hydroxy-propylmethylcelluloses (HPMC), hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, alkylcelluloses, hydroxy-alkylcelluloses hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans such as, for example, guar and carob flour, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch or starch derivatives or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, additionally comprising step of administering said material orally, topically, intranasal, vaginally, rectal, ocular and parenteral routes or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said API is released at temperature of 36-42° C.; pH in the range of 5.5-8.0, at a rate of 80% in a time range of 3 to 30 hours.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said API is released at temperature of 36-42° C.; pH in the range of 1-8.0, at a rate of 80% in a time range of 2 to 4 weeks.

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It is a further object of this invention to disclose such a method as defined in any of the above, wherein said API is released at temperature of 36-42° C.; pH in the range of 1-9.0, at a rate of 80% in a time range of 3 to 30 hours.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said API is dissolved, suspended and/or solid, amorphous or crystalline form.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said API is provided in various particle sizes, in unground, ground or in micronized form.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said material is administered topically; further wherein said API is selected from a group consisting of Antineoplastic drugs; Chemotherapeutic agents; Anti-infective agents, Antimicrobial drugs, Antiparasitic agents, Antivirals; Drugs acting on the blood and blood forming organs, Antihemorrhagics, Antithrombotic agents, antianemic drugs, Dermatologic drugs, antifungals, antiseptic, Genito-urinary system drugs, Gastrointestinal system, antiobesity, acid related disorders, Metabolism drugs, Anti-inflammatory product, Musculoskeletal system acting drugs; Neurological drugs, Respiratory drugs, Cardio-vascular drugs, Otolological drugs, Anti-infective drugs, Corticosteroids drugs, Analgesics and anesthetics drugs, GeneTherapy, Antiparasitics drugs, Growth factors, VEGF, Inhibitory factors, LIF or any combination thereof.

It is a further object of this invention to disclose such a method as defined in any of the above, additionally comprising step of providing said material with at least one selected from a group consisting of Poly (propylene oxide)—PPO, Poly (lactide-co-glycolic acid)—PLGA, Poly (N-isopropylacrylamide)—PNIPAM, Poly (propylene fumarate)—PPF, Poly (urethane)—PU, Poly (organophosphazene)—POP, Poloxamers of the type PEO-PPO-PEO (Poly (ethylene oxide), Poly (propylene oxide), Poly (ethylene oxide)) such as poloxamer 68, 88, 98, 108, 124, 127, 188, 237, 338 and 407, Stearic Acid, Poly (acrylic acid), Glyceryl Stearate, Cetearyl Alcohol, Sodium Stearoyl Lactylate, Hydroxy-Lenolin or any combination thereof.

It is a further object of this invention to disclose such a method, wherein said biocompatible sustained-release material is the biocompatible sustained-release material as defined in any of the above.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said internal body cavity is at least one selected from a group of internal cavities that includes, among others, the urinary bladder, mouth, nasal and paranasal sinus, gallbladder, esophagus, rectum, lungs, vagina, uterus, stomach, renal pelvis, pleura, abdomen, peritoneum, pelvis, liver, kidney, heart, intestine, brain, vertebral column, etc.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said therapeutic agent is a therapeutic agent for treatment of superficial bladder cancer.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of introducing said biocompatible sustained-release material into said internal body cavity further comprises a step of introducing said biocompatible sustained-release material into said internal body cavity via a catheter.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of releasing said therapeutic material into said internal body

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cavity further comprises a step of dissolving said biocompatible sustained-release material in body fluid within said internal body cavity, whereby said therapeutic agent is released from said biocompatible sustained-release material.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying force to said material further comprises a step of filling said catheter balloon with water and positioning the patient to utilize the gravitational forces directly toward the target tissue during the solidification of the material and cause optimal adhesion to that target tissue.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying gravitational force to said material further comprises a step of changing the position of the patient before applying partial doses of material to enable substantially full coating of the whole targeted internal cavity surface.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying force to said material further comprises a step of filling said balloon with a liquid denser than water.

It is a further object of this invention to disclose such a method, wherein said liquid denser than water comprises a solution of salt in water, said solution having a density greater than 1.0 g/cm<sup>3</sup>.

It is a further object of this invention to disclose such a method, wherein said liquid denser than water comprises a solution of glucose in water, said solution having a density greater than 1.0 g/cm<sup>3</sup>.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying force to said material further comprises steps of inserting a first magnetic means into said balloon; and, applying a second magnetic means such that the magnetic attraction of said first magnetic means and said second magnetic means causes said first magnet to move within said balloon, whereby said attraction applies force to at least part of the internal surface of said internal cavity.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying force to said material further comprises steps of introducing a ferromagnetic liquid into said balloon; and, applying magnetic means such that the magnetic attraction of said magnetic means and ferromagnetic particles suspended within said ferromagnetic liquid causes said ferromagnetic particles to move within said balloon, thereby applying force to at least part of the internal surface of said internal cavity.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying force to said material further comprises steps of introducing into said balloon a substance chosen from (a) a constant or electric magnet, (b) a piece of ferromagnetic material, and (c) a ferromagnetic liquid; placing the patient within an MRI apparatus; and, activating said MRI apparatus such that the magnetic field of said MRI apparatus causes said substance to move within said balloon, thereby applying force to at least part of said internal cavity.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein the solubility of said material is sufficiently high that said material will completely degrade in less than 4 weeks after incorporation into an internal body cavity.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said material

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is characterized by a viscosity of less than 200 Pa·s at a range of 10° C. to 25° C. and greater than 3000 Pa·s at a range of 35° C.-37° C.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said material is characterized by a viscosity of less than 200 Pa·s at 10° C. and greater than 3000 Pa·s at 37° C.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein the instillation temperature of said material is between 4° C. and 60° C.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said material comprising 20-30% Pluronic F-127; 0-1.8% PEG-400; 0.1%-0.3% HPMC; an effective amount of a therapeutic agent; and the balance water.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said material comprising 20-30% Pluronic F-127; 0-2.5% PEG-400; 0.05%-0.5% HPMC; an effective amount of a therapeutic agent; and the balance water.

It is a further object of this invention to disclose such a method as defined in any of the above, additionally comprising step of providing said material as biological glue.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein the weight of the balloon filled with a liquid denser than water is used for the application of the gel (utilizing its gravity).

#### BRIEF DESCRIPTION OF THE FIGURES

The invention disclosed herein is described with reference to the figures, in which:

FIG. 1 presents a flow diagram of the creation of a hydrogel composition in a drug delivery system for treatment of internal cavities;

FIG. 2 presents schematic illustrations of micellar phases, formed by the polymer herein disclosed with increasing temperature;

FIG. 3a-d presents graphs illustrating the MMC cytotoxicity when different MMC concentrations are used in saline and in DTC-2 respectively;

FIG. 4a-b presents graphically the results of a study of the effect of botulinum toxin gel on contraction of animal bladder as model for overactive bladder contraction;

FIG. 5a-b presents graphs representing results of measurements of rheological parameters of the material according to several embodiments of the invention herein disclosed;

FIG. 6 presents a graph showing the delivery of MMC to pig bladder tissue by use of a gel according to one embodiment of the present invention;

FIG. 7 presents results of measurements of in vitro release of Lidocaine hydrochloride (10 and 20 mg/ml) from reverse thermal hydrogel (including 27% Ethylene Oxide/Propylene Oxide Block Copolymer, 1% PEG-400, 0.2% Hydroxypropylmethyl cellulose in water) and Cephalexin (1 mg/ml) from reverse thermal hydrogel (20.0% Pluronic F-127, 10% Pluronic F-68 (10.0%) 1.0% PEG-400 0.4% CMC sodium in water; and,

FIG. 8 shows results for the dissolution rate of hydrogels according to several different embodiments of the invention.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the following description, various aspects of the invention will be described. For the purposes of explanation,

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specific details are set forth in order to provide a thorough understanding of the invention. It will be apparent to one skilled in the art that there are other embodiments of the invention that differ in details without affecting the essential nature thereof. Therefore the invention is not limited by that which is illustrated in the figure and described in the specification, but only as indicated in the accompanying claims, with the proper scope determined only by the broadest interpretation of said claims.

As used herein, the term "internal cavity" is used to describe parts in the body that are either accessible through an orifice—e.g., mouth, bladder, intestine, esophagus, rectum, lungs, vagina, stomach, renal pelvis, etc.—or by way of minimally invasive, surgery—e.g., pleura, abdomen, peritoneum, pelvis, etc. The definition includes artificially made or enlarged cavities in adipose tissues and fibrous capsules in internal organs such as the kidney, heart, intestine, etc. that are accessible by image guided laparoscopic techniques.

As used herein, the term "DTC" is used to refer generically to the materials disclosed in the present invention. The terms "DTCx" and "DTC-n" (where n is an integer) are used to refer to particular embodiments, either generically (DTCx) or specifically (e.g. DTC-2).

The present invention provides a bioerodible, biocompatible gel mixed with an active agent, such as chemotherapy agent like MMC or gemcitabine, or immunotherapy such as BCG (*bacillus Calmette-Guérin*), which is inserted into the upper urinary tract via a designated catheter, solidifies and forms a drug reservoir at the destined treatment area such as the renal pelvis. The diffusion of the drug from the gel and the erosion of the gel by the urine or the biodegradability of the gel, deliver drug to the tissue-producing prolonged high topical drug concentration but low systemic exposure. This, the system increases bioavailability, reduces toxicity and improves treatment efficacy. Furthermore, loading the material with significant concentration of chemotherapy agent and applying the material directly over a tumor for a prolonged duration, may ablate non-resected tumors that are in close contact with the material.

The present invention provides a design of such gel compositions that is based on the characteristics of the internal cavities to be treated and the specific requirements for said treatments in order to determine the required properties of hydrogel systems that can satisfy all these requirements. A flow diagram for creation of hydrogel composition is illustrated in FIG. 1. This structured set of gel properties enables the formulation of gel systems for optimal drug delivery. The present invention provides a structured design and test flow that assures optimal hydrogels for optimal treatments.

In some embodiments, the present invention additionally provides a bioerodible, biocompatible hydrogel that is mixed with a neurological drug such as botulinum toxin, is inserted into the bladder, solidifies and forms a drug reservoir inside the bladder. The erosion of the material in the urine, promotes topical drug delivery and increases the drug affinity to the bladder wall tissue producing high topical drug concentration in the bladder wall and at the same time keeps a low systemic exposure. The system provides drug delivery to the entire bladder resulting in total tissue contact with the delivered neurological drug as opposed to delivery induced by local injections.

The invented material includes a mixture of hydrogel with botulinum toxin (A, B, C1, D, E, F and G and equivalent neurological drugs) for the treatment of disorders characterized by bladder spasms (eg. urge incontinence due to unstable bladder or unstable detrusor, sphincter or neuro-

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genic bladder, etc.). The hydrogel mixed with botulinum toxin will be instilled into the bladder without injections into the bladder tissue and its effect will be.

The present invention also includes the use of the novel pharmaceutical formulation or admix for producing medicaments which are intended for the treatment and/or prevention of disorders in humans. These systems contain drugs embedded in a slowly degrading biocompatible admix and are combined with administering means, so that the materials can be introduced in a minimally invasive manner into a body cavity and provide a prolonged exposure of the cavity tissue to the drug, thus improving the treatment efficacy in terms of improved therapeutic effect of the drug and reduced tissue damage. The admix/mixture is biocompatible and dissolves in body fluids such as urine, serous fluids or lymphatic fluids, and then it is expelled from the body.

The aim of the prolonged exposure of target tissue to drugs released from the coating is to enhance the efficacy of the drug in topical treatment of that target tissue, while reducing potential systemic adverse effects to other organs. As a specific example, the aim of the prolonged exposure of cancer cells to an anticancer drug released from the coating is to enhance the efficacy of the drug in killing cancer cells and, therefore, potentially reduce the recurrence rate of cancer tumors, while reducing the systemic effect of chemotherapy on other parts of the patient body.

The homogeneous coating obtained in the invention disclosed herein, i.e., a solidified, unified and homogeneous layer that provides continuous sustained release of therapeutic agents upon the inner surface of an internal body cavity, as herein disclosed, has to the inventors' knowledge never been produced or used clinically.

Thus, it is one object of the present invention to provide a material that includes active pharmaceutical ingredients (APIs) as a part of its basic formulation.

The current invention provides a platform for the redesign of drugs to make them suitable for topical administration. Company studies demonstrated solubility and first order sustained release of Mytomicin C, Doxorubicin and Gemcitabin (groups 1 & 2), Abamectin (group 3), exogenous glycosaminoglycan, group 4), Naproxen (group 5), lidocaine and voltaren (group 6).

Among the drugs that can be administered topically are drugs that belong to the following families:

1. Antineoplastic drugs
2. Chemotherapeutic agents
3. Anti-infective agents (e.g. Antimicrobial drugs, Antiparasitic agents, Antivirals)
4. Genito-urinary system drugs
5. Anti-inflammatory products
6. Analgesics
7. Musculoskeletal system acting drugs
8. Drugs acting on the blood and blood forming organs (Antihemorrhagics, Antithrombotic agents, antianemic drugs)
9. Dermatologic drugs (antifungals, antiseptic)
10. Gastrointestinal system (antiobesity, acid related disorders)
11. Metabolism drugs
12. Neurological drugs
13. Respiratory drugs including nasal drugs
14. Cardio-vascular drugs
15. Otological drugs
16. Anti-infective drugs
17. Corticosteroids drugs
18. Analgesics drugs
19. Antiparasitics drugs
20. Anesthetic Drugs



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In other cases, the topical treatment is just evolving:

21. Growth factor (e.g., for treatment of heart muscle ischemia)
22. Gene Therapy agents
23. Mucin
24. Hyaluronic Acid

Drugs can be embedded as part of the invented materials as a single therapeutic agent or as a combination. As an example, a mixture containing exogenous glycosaminoglycan and Naproxen can be combined in a specific material for the treatment of interstitial cystitis for alleviating the inflammation symptoms and replacing the damaged mucosal lining of the urinary bladder cavity that is typical for this disease.

The present invention provides a formulation/mixture which release active ingredients (API) in a controlled fashion over a prolonged period. It is further an object of the present invention to provide medicament formulations with particular release profiles through which the prior art problems. As an example an average release rate between 80% in 6 hours and 80% in 24 hours is maintained.

As standard, chemotherapy drugs are administered at a maximal concentration level that is tolerable by patients. The present invention study results demonstrate that a further improvement in efficacy can be gained by increasing the exposure time to chemotherapy drugs. This is at the core of the present invention.

In addition, the use of such formulation allows reduction of the frequency of administration thus leads to improved patient's compliance.

A longer exposure time of the API has distinct advantages and it is expected that a prolonged exposure with an API on use of a medicament with controlled release of active ingredient makes it possible to prolong substantially the time window in which improved therapy can be achieved. The use of the novel medicinal forms with controlled release of active ingredient is expected to achieve substantially more constant drug levels and avoid the occurrence of level peaks, thus improving for example the therapeutic efficacy and reducing the frequency and intensity of unwanted side effects.

In addition, the use of such admix/formulation/mixture allows the frequency of administration to be reduced and thus leads to improved acceptance and compliance by the patient.

It is expected as well that controlled-release of APIs prolong exposure without the occurrence of an increase in side effects, an adverse effect on reliability and safety of therapies. According to a preferred embodiment of the present invention the admix/formulation/mixture described above, is for example in the form of active ingredient-containing hydrogels. These diffusion-controlled systems may be completely diluted in the hydrogel admix/formulation/mixture or can be multiparticulate, i.e. they may consist of a large number of coated cores such as, for example, of microencapsulated APIs, where appropriate together with conventional excipients and carriers, as defined below for example, is applied and subsequently coated with a diffusion coating which may comprise plasticizers and other excipients. The diffusion-controlled systems according to the invention may additionally consist of homogeneous active ingredient-containing cores which are produced for example by granulation, rotor granulation, fluidized bed agglomeration, tableting, wet extrusion or melt extrusion, where appropriate with spheronization, and are coated with a diffusion coating which may comprise plasticizers and other excipients.

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According to one embodiment, the present invention may provide a combination of APIs, one or more diluted or suspended in the gel and one or more microencapsulated for slower release effect. For example, an anesthetic like lidocaine dissolved in the admix/formulation/mixture for immediate anesthetic effect and encapsulated MMC for cancer treatment that is released after the bladder wall is insensitive and the patient can stand the MMC therapy.

In a preferred embodiment of this invention, the active ingredient-containing particles comprise excipients such as, for example, acids or buffer substances which modify the pH and thus contribute to reducing the dependence of the release of active ingredient on the pH of the release medium.

According to a preferred embodiment of the present invention the material/formulation/mixture described above, additionally comprises at least one ingredient selected from:

- (a) adhesive and thickening compounds;
- (b) bonding agents;
- (c) pH-modifying substances;
- (d) diffusion coating;
- (e) plasticizers;
- (f) Tight junction modifiers & permeability enhancers;
- (g) matrix permeability increasing components;
- (h) swellable excipients matrix-forming polymers;
- (i) diffusion-controlled or pulsatile formulations; and,
- (j) reverse thermal gelation agents.

The adhesive and thickening compounds preferably used in the production of coated neutral pellets (e.g. consisting of sucrose, microcrystalline cellulose, citric acid) are polycarboxophil (polymer of acrylic acid crosslinked with divinyl glycol), hydroxypropylmethylcellulose (HPMC) and polyvinylpyrrolidone (PVP). It is likewise possible to employ other naturally, synthetic or partially synthetic polymers such as, for example methylcellulose (MC), hydroxypropylcellulose (HPC), other hydroxyalkylcelluloses and hydroxyalkylmethylcelluloses, carboxy-methylcelluloses and salts thereof, polyacrylic acids, polymethacrylates, gelatin, starch or starch derivatives, as well as gums like guar gum and xanthan gum.

The bonding agents employed for the production of active ingredient-containing microcapsules are for example polycarboxophil, cellulose, microcrystalline cellulose, cellulose derivatives such as, for example, HMPC, HPC and low-substituted hydroxypropylcellulose (L-HPC), dicalcium phosphate, lactose, PVP and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPM-CAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides (e.g. alginic acid, alginates, galactomannans) waxes, fats and fatty acid derivatives. The pH-modifying substances such as, for example, acids, bases and buffer substances are incorporated into the active ingredient-containing core. Addition of these substances makes it possible to reduce markedly the pH-dependence of the release of the APIs. Examples of suitable excipients which modify the pH in the active ingredient-containing cores are: adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, toluenesulphonic acid, trometamol, tartaric acid. Citric acid, succinic acid, tartaric acid, potassium hydrogen tartrate are preferably employed. Particularly suitable for producing the diffusion coating are ethylcelluloses and polymethacrylates such as, for example,



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EUDRAGIT® NE, EUDRAGIT® RS and RL. However, other materials such as, for example, cellulose acetate and cellulose acetate butyrate can also be employed as film-forming diffusion-controlling polymers. Examples of plasticizers used are citric acid derivatives (e.g. triethyl citrate, tributyl citrate, acetyl triethyl citrate), phthalic acid derivatives (e.g. dimethyl phthalate, diethyl phthalate, dibutyl phthalate), benzoic acid and benzoic esters, other aromatic carboxylic esters (e.g. trimellithic esters), aliphatic dicarboxylic esters (e.g. dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters), glycerol monoacetate, glycerol diacetate or glycerol triacetate, polyols (e.g. glycerol, 1,2-propanediol, polyethylene glycol of varying chain length), fatty acids and derivatives (e.g. glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol) and fatty acid alcohols (e.g. cetyl alcohol, cetylstearyl alcohol).

The nature and amount of the plasticizer are chosen so that the above-defined release according to the invention and the necessary stability of the medicinal forms is achieved. The proportion of the plasticizer is from 0 to 50%, preferably 0 to 35%, particularly preferably 0 to 25% based on the mass of the hydrogel composition.

The release rate according to the invention is controlled by the gel composition. Certain components may increase the permeability of the admix/formulation/mixture including water-soluble polymers such as, for example, polyethylene glycols, PVP, PVA, HPMC, HPC, hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans or other soluble substances such as, for example, urea, salts (sodium chloride, potassium chloride, ammonium chloride, etc.), sugars (sucrose, lactose, glucose, fructose, maltose etc.) and sugar alcohols (mannitol, sorbitol, xylitol, lactitol, etc.). Based on the mass of the hydrogel, the amount of the water-soluble polymers ranges from 0 to 50%, preferably 0 to 35%, particularly preferably 0 to 20%, increasing permeability components may be employed.

A further aspect of the present invention are coated admix/formulation/mixture which comprise one or more swellable excipients which, on penetration of liquid through the membrane, swell greatly and, through the swelling and volume expansion, cause the coating to split. The splitting of the coating makes it possible for the medicinal substance to be released from the admix/formulation/mixture, usually in pulsatile form. Swellable excipients which these formulations may comprise are, for example, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl starch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC). Examples of suitable coating materials are cellulose acetate, ethylcellulose and polymethacrylates.

The described diffusion-controlled or pulsatile formulations can be employed directly and unmodified as medicinal form. However, they may also be further processed, where appropriate with addition of excipients, to the final admix/formulation/mixture. In order to achieve a desired release profile it is also possible to combine different coated formulations in one medicinal form, and administration of an initial dose can take place for example by combination with rapid-release formulation particles, e.g. uncoated pellets, granules or powder.

In a further embodiment of the admix/formulation/mixture containing the controlled release ingredient. These so-called admix/formulation/mixture release the active ingredient by diffusion and/or erosion.

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The mass ratio of active ingredient to the total mass of the admix/formulation/mixture in these novel formulations is in the range from 1:1 to 1:10,000, preferably in the range from 1:2 to 1:1,000.

admix/formulation/mixture which can be employed are water-soluble, water-swellaable or water-insoluble substances. The novel formulations preferably comprise one or more water-swellaable polymers.

Preference is additionally given to medicinal preparations in the context of this invention which comprise water-soluble, hydrogel-forming polymers, these polymers having a nominal viscosity of at least 0.015 Pa s, preferably at least 0.050 Pa s (measured as 2% strength aqueous solution at 20° C.).

A preferred family of candidates to be utilized as a basis for obtaining said hydrogel is group of tri-block copolymers designated as PEG-PPG-PEG (PEG=Polyethylene glycol and PPG=Polypropylene glycol) and called Poloxamers, that produce reverse thermal gelation compositions, i.e., with the characteristic that their viscosity increases with increasing temperature up to a point from which viscosity again decreases. In particular, Poloxamer 407 possesses a gelling temperature which is above 10° C. but below the human body temperature, i.e., 37° C. This characteristic may confer the ability of a composition containing the compound to be injected or infused in liquid state into a bodily inner cavity at a low temperature and, afterwards, as the composition warms, it solidifies into a gel, thus stabilizing upon the wall of the inner body cavity.

This characteristic has allowed Poloxamer 407 (PF-127) to be used as a carrier for most routes of administration including oral, topical, intranasal, vaginal, rectal, ocular and parenteral routes.

Poloxamer 407 (PF-127) is a nonionic surfactant composed of polyoxyethylene-polyoxypropylene triblock copolymers in a concentration ranging from 20-30%. At low concentrations (10-4-10-5%) they form monomolecular micelles, but higher concentrations result in multimolecular aggregates consisting of a hydrophobic central core with their hydrophilic polyoxyethylene chains facing the external medium. Micellization occurs in dilute solutions of block copolymers in selected solvents above the critical micellar concentration, at a given temperature. At higher concentrations, above a critical gel concentration, the micelles can order into a lattice.

Aqueous solutions of poloxamers are stable in the presence of acids, alkalis, and metal ions. Commonly used poloxamers include the 88 (F-68 grade), 237 (F-87 grade), 338 (F-108 grade) and 407 (F-127 grade) types, which are freely soluble in water. The "F" designation refers to the flake form of the product. PF-127 has a good solubilizing capacity, low toxicity and is, therefore, considered a good medium for drug delivery systems.

PF-127 is a commercially available polyoxyethylene-polyoxypropylene triblock copolymer that possesses a general formula E101 P56 E101, with an average molar mass of 13,000. It contains approximately 70%, ethylene oxide, which accounts for its hydrophilicity. It is one of the series of poloxamer ABA block copolymers. As said above, PF-127 aqueous solutions of 20 to 30% w/w have the interesting characteristic of reverse thermal gelation, i.e., they are liquid at refrigerated temperatures (4-5° C.), but gel upon warming to room temperature. The gelation is reversible upon cooling. This phenomenon, therefore, suggests that when poured onto the skin or injected into a body cavity, the gel preparation will form a solid artificial barrier and a

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sustained release depot Furthermore, PF-127 has been reported to be the least toxic of commercially available copolymers.

Water-soluble or water-swellaable matrix-forming polymers preferably employed are hydroxy-propylmethylcelluloses (HPMC), hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, other alkylcelluloses, hydroxy-alkylcelluloses and hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans such as, for example, guar and carob flour, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch or starch derivatives and mixtures of these substances.

In this connection, the admix/formulation/mixture according to the invention should preferably comprise at least 0.1-2.0% of a hydroxypropylmethylcellulose type whose nominal viscosity (measured as 2% strength aqueous solution at 20° C.) is at least 0.015 Pa s, preferably at least 0.050 Pa s. HPMC types preferably used have a degree of substitution of methoxy groups of 16.5-30%, particularly preferably 19-30%, and a degree of substitution of hydroxypropoxy groups of 4-32%, particularly preferably 4-12%.

In a particularly preferred embodiment of this invention, substances which control the pH in the admix/formulation/mixture are incorporated into the admix/formulation/mixture. The addition of such pH-modifying excipients and/or the addition of substances which dissolve or are dissolved out of the admix/formulation/mixture as the pH increases, and thus increase the porosity or permeability of the admix/formulation/mixture and/or promote erosion of the admix/formulation/mixture, makes it possible to achieve a virtually pH-independent release for these preferred embodiments of the present invention.

Examples of suitable excipients which can be added to the admix/formulation/mixture according to the invention to achieve release which is as far as possible pH-independent are the following substances: adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, cellulose phthalates, in particular cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate, cellulose succinates, in particular cellulose acetate succinate and HPMCAS, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, polymethacrylates (e.g. EUDRAGIT® types), toluenesulphonic acid, trometamol, tartaric acid. Citric acid, succinic acid, tartaric acid, HPMCAS, and polymethacrylates (e.g. EUDRAGIT® L) are preferably employed. If these excipients are present in the admix/formulation/mixture according to the invention, they are typically added in a proportion of from 10 to 50% based on the total mass of the admix/formulation/mixture.

Examples of plasticizing excipients in the hydrogel formulation are propylene glycol, glycerol, triethylene glycol, butanediols, pentanols, such as pentaerythritol, hexanols, long-chain alcohols, polyethylene glycols, polypropylene glycols, polyethylene/propylene glycols, silicones, phthalic acid derivatives (e.g. dimethyl phthalate, diethyl phthalate, dibutyl phthalate), benzoic acid and benzoic esters, other aromatic carboxylic esters (e.g. trimellithic esters), citric acid derivatives (e.g. triethyl citrate, tributyl citrate, acetyl triethyl citrate), aliphatic dicarboxylic esters (e.g. dialkyl

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adipates, sebacic esters, in particular diethyl sebacate, tartaric esters), glycerol monoacetate, glycerol diacetate or glycerol triacetate, fatty acids and derivatives (e.g. glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol), fatty acid alcohols (e.g. cetyl alcohol, cetylstearyl alcohol), sugars, sugar alcohols and sugar derivatives (e.g. erythritol, isomalt, lactitol, mannitol, maltitol, maltodextrin, xylitol). The concentration of plasticizers is normally from 0 to 30%, preferably from 0 to 20% based on the total mass of the gel.

Examples of further suitable water-swellaable polymers which may be incorporated in the hydrogel are high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl starch, low-substituted hydroxypropylmethylcellulose (L-HPC), poly(hydroxyalkyl methacrylate), alginates and galactomannans and mixtures thereof.

The present invention further relates to the combination of formulations with different release properties, e.g. rapid-release and slow-release, in one medicinal form.

As described above, according to one embodiment of the present invention a admix/formulation/mixture which release active ingredients (API) in a controlled fashion over a prolonged period is provided.

If necessary, the pH can be adjusted to 1-8.0 with a buffer composition. The release is carried out at a temperature of 36-42° C.

If necessary, the pH can be adjusted to 1-5.5 with a buffer composition. The release is carried out at a temperature of 36-42° C.

If necessary, the pH can be adjusted to 5.5-9.0 with a buffer composition. The release is carried out at a temperature of 36-42° C.

The amount of active ingredient determined in this way is converted into percent by mass of the amount of active ingredient employed.

The average release rate in the context of the present invention is defined via the time until the release of active ingredient reaches 80%, whereas the initial release describes the percentage release of active ingredient after 30 minutes.

The admix/formulation/mixture according to the invention with controlled release of active ingredient preferably have an average release rate of 80% in the time interval between 3 and 20 hours (80% in 3 hours and 80% in 20 hours).

The admix/formulation/mixture according to the invention with controlled release of active ingredient preferably have an average release rate of 80% in the time interval between 2 and 4 weeks (80% in 2 hours and 80% in 4 weeks).

In a particularly preferred embodiment of the medicament formulations with controlled release of active ingredient of the present invention, the formulation has an average release rate of 80% in the period from 3 and 18 hours and an initial release not exceeding 65% of the active ingredient in the first 30 minutes of release.

The admix/formulation/mixture according to the present invention can be formulated so that a relative low initial release of 0 to 30% in the first 30 minutes or a relative high initial release of 30 to 60% of the medicinal substance in the first 30 minutes of medicinal substance release is achieved.

In a preferred embodiment of the admix/formulation/mixture of the present invention is characterized by an

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average release rate of 80% in the period from 4 to 18 hours, this has a relatively low initial release of 0 to 25% in the first 30 minutes of release.

Another preferred configuration of the medicament formulations with controlled release of active ingredient has an average release rate of 80% in the period from 3 to 16 hours and is distinguished by a relatively high initial release of 35 to 60% in the first 30 minutes of release of active ingredient.

It should be emphasized that the admix/formulation/mixture with controlled release of active ingredient of this invention refers to all formulations in which the release of active ingredient is modified so that it takes place with a slower delivery rate than from rapid-release medicinal forms such as, for example, a conventional instillation procedure in the case of bladder cancer treatment.

Furthermore, the admix/formulation/mixture with controlled release of active ingredient of the present invention also include formulations with delayed release in which the delivery of the active ingredient is modified so that the release starts at a later time than with a conventional rapid-release medicinal form. The subsequent release from a delayed-release medicinal form may also take place in controlled fashion with a reduced release rate.

The admix/formulation/mixture according to the invention with controlled release of active ingredient also include formulations with pulsatile release, where the delivery of active ingredient takes place intermittently, and formulations in which different principles of controlled delivery of active ingredient are combined.

The admix/formulation/mixture of this invention additionally include also medicament formulations which comprise part of the active ingredient in rapid-release form and a further part of the active ingredient in controlled-release form.

The medicament formulations according to the invention may comprise the active ingredient is dissolved in, suspended and/or solid, amorphous or crystalline form. The active ingredient can be employed in various particle sizes, e.g. in unground, ground or in micronized form, to produce the admix/formulation/mixture according to the invention with controlled release of active ingredient.

According to one embodiment of the present invention provides a hydrogel composition that is intended to be used as a topical therapeutic agent, applied topically. Thus, it would be useful to have a device that allows the application of such said hydrogel composition once accessing a body organ (inner cavity) through an orifice (either natural or artificial), so as to allow the coating of the inner wall of the organ with said hydrogel gel. Such hydrogel composition will adhere well to said wall and will (i) allow the controlled release of the drug or drugs; (b) will enable the gradual dilution of the hydrogel; and, (c) expelled from the body in a reasonable period of time (e.g., 24 hrs).

According to another embodiment, cell line studies (see below) performed by the inventors of the present invention, demonstrate up to  $\times 30$  higher cell kill when cell lines are exposed to MMC for  $\times 10$  longer time or to  $\times 10$  higher concentrations.

As standard, chemotherapy drugs are administered at a concentration level that is tolerable by patients. The present invention study results demonstrate that a further improvement in efficacy can be gained by increasing the exposure time to chemotherapy drugs. This is at the core of the present invention's concept.

Several of the present invention's materials incorporate a variety of chemotherapy drugs for the treatment of bladder

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cancer—as non-limited examples, Mitomycin C, Doxorubicin, Valrubicin and Gemcitabine are used with DTCx materials.

The present invention attempts to a) bring the largest part of anticancer drug to contact with the tissue of the bladder wall and b) prolong the contact duration. These measures will probably improve the treatment efficacy.

The present invention provides sustained release materials that are efficient for indications such as the non-limited example of interstitial cystitis. The DTC material is designed to stay in the bladder for a week and the medical drugs used are a combination of Heparin and NSAID (Non-Steroidal Anti-Inflammatory Drug).

Prolonging the duration of tissue exposure to drug and significantly delaying the expelling of the drug from the bladder result in a dramatic improvement of the drug efficacy. The composition provided by the present invention, which furnishes a homogeneous, well-adhered coating of the bladder inner wall, has the capability to provide such prolonged drug release and overcome the difficulties of adherence to the internal wall of the bladder, such that the chemotherapy drug treatment duration is significantly prolonged and the cancer treatment efficacy is improved.

This solidified, unified and homogeneous layer coating of the bladder wall possesses numerous advantages. Foremost is the ability to continuously release anticancer agents over a prolonged period of time, as opposed to the gold standard treatment of introducing a fixed amount of drug for a short and indeterminate period, which is expelled from the bladder when the patient first urinates after the instillation induction.

A pre-clinical study of sows demonstrated a 20:1 higher level of chemotherapy in the bladder, six hours after instillation with the invented material compared to regular instillation of the same amount of chemotherapy.

Interestingly, the developed polymeric materials allow their comfortable administration through a thin tube, for example a urethral catheter, without exerting more than the common pressure required to inject a saline through such a device; and at the same time, as the liquid polymer settles upon the bladder wall, it solidifies creating a gelatinous film that then gradually releases the therapeutic ingredient upon said bladder wall.

This feature is of fundamental importance and is enabled by the fact that the polymeric composition was designed so as to possess reverse thermal gelling properties (see below), that is, to possess low viscosity at low temperatures (say, below 15° C.) and increase dramatically its viscosity as its temperature increases due to the body heat.

The coating layer created on the tissue of the internal cavity, disclosed in the present invention, is essentially a unified and homogeneous layer of substrate applied and affixed to organ tissue.

Beyond maximization of the area of the tissue that is exposed to drug, this coating can also be used to control the distance between organs. Following are several examples:

Fixation and treatment of pleura. A common condition in several lung and heart diseases is pleural effusion, when serous fluids, pus or chyle accumulate into the space between the visceral pleura and the parietal pleura layers surrounding the lungs—condition called hydrothorax or pleural effusion. Ordinarily there is little space between these layers, but certain malignancies may cause the accumulation of fluids at excessive levels that can impair breathing and cause severe outcome. A standard treatment for larger effusions is the insertion of intercostals drain, often accompanied



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by surgical pleurodesis—in which the two pleural surfaces are scarred to each other so that no fluid can accumulate between them—or even open pleurectomy. This surgical joining of the layers is not always successful, but when it does—it is permanent.

A material of the present invention can be administered into the pleura cavity to adhere to the pleura layers and provide both a mechanical bond and sustained release of drug for treatment of the underlying malignancy (e.g. Tetracycline antibiotic for bacterial infection, or NSAID such as Naproxen to treat fever and inflammation. The pleura-hydrogel material is inserted into the pleura space via a catheter or trocar, as non-viscous liquid at a temperature that is below 15° C. and adheres to the surrounding tissue as it heats to body temperature. The material is designed to dissolve gradually into the pleura fluids over less than a week and both maintain mechanical support and release the drugs during that whole period. The main advantages of this method are the combination of this procedure ability to replace a more invasive one, the natural and easy application, the reduction of tissue damage, the soothing effect of the hydrogel and the enhanced healing effect of the sustained release of anti-inflammatory agents.

Fixation of organs and prevention of tissue adhesion in the abdomen during laparoscopy.

A material of the current invention can be introduced into the abdomen cavity and provide mechanical support to the target organs in the position that best fits the surgical procedure. The peritoneum-hydrogel material can be inserted into the peritoneum cavity via endoscope working channel, a catheter or trocar, as non-viscous liquid at a temperature that is below 15° C. and adhere to the surrounding tissue as it heats to body temperature. The material is designed to dissolve gradually into the pleura fluids over less than a week and both maintain mechanical support of the organs for several hours and release the drugs during a longer period.

Similar method, but with different materials can be used to prevent the adhesion of tissues between organs in the treated area, which may often occur during laparoscopic surgery.

The main advantages of this method are the combination of its ability to replace a more invasive procedure, the reduction of tissue damage, the soothing effect of the hydrogel and the enhanced healing effect of the sustained release of anti-inflammatory agents. A further advantage is the prevention of the need to remove the fixation surgically because of the natural degradation and expelling of the invented material from the treated area.

The release of drug from the admix/formulation/mixture occurs due to two phenomena that take place simultaneously after the gel is applied upon the bladder wall: (1) Drug diffusion from the gel to the aqueous medium (urine); (2) Dissolution of the gel itself in the aqueous medium. We may consider two extreme cases in which the drug either diffuses very fast from the gel to the urine medium, or diffuses very slowly. In the first case, the gel will be depleted very fast of drug so the bladder wall coated by the gel will “see” a low concentration of drug almost from the beginning. On the other hand, the concentration of drug in the urine will be higher and that is the concentration that uncoated parts of the bladder will see. If the case is the second (very slow release rate), the bladder wall coated by the gel will “see” a more or

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less high concentration of drug for a long time, in fact, until the whole of the gel is dissolved in the urine phase. These two separate but intertwined factors, which we call “two clocks”, serve to design different therapies utilizing different drugs and tailor-made polymeric carriers according to the medical needs.

A water-based admix/formulation/mixture is made of large molecules that create spaces between the molecules that serve as matrix nodes. These spaces can be filled with drug molecules in a way that enables their diffusion into aqueous solution. The amount of drug molecules that can be held in a admix/formulation/mixture depends on the three-dimensional shape of the molecules as they are positioned in the admix/formulation/mixture. The diffusion rate depends on them admix/formulation/mixture three dimensional structure and packing factor.

DTCx materials are designed according to the three dimensional shapes of the admix/formulation/mixture and the compound molecules. admix/formulation/mixture design that uses even, large molecules, may store a high amount of drug, but will also enable fast diffusion out of the admix/formulation/mixture.

Admix/formulation/mixture design that combines larger and smaller molecules enables lower diffusion coefficients—leading to longer release durations—and, with some sacrifice of the included space volume.

Design of the admix/formulation/mixture that should store drugs for longer times is based on a ‘matrix of polymer matrix’—i.e., higher order polymers. These structures can store drug molecules that start to diffuse only after the higher order structure is at least partially dissolved. Poloxamer 407 (PF-127) is a nonionic surfactant composed of polyoxyethylene—polyoxypropylene copolymers. In general, poloxamers are composed of white, waxy, freeflowing granules that are practically odorless and tasteless. The “F” designation refers to the flake form of the product. PF-127 is recognized as a pharmaceutical substance (Pharmacopeia/NF). It has a good solubilizing capacity, low toxicity and is therefore considered a good medium for drug delivery systems.

As described above, PF-127 is a commercially-available polyoxyethylene-polyoxypropylene triblock copolymer of general formula E101 P56 E101, with an average molar mass of 13,000. It is one of the series of poloxamer ABA block copolymers.

PF-127 is more soluble in cold water than in hot water as a result of increased salvation and hydrogen bonding at lower temperatures. PF-127 aqueous solutions of 20 to 30% w/w have the interesting characteristic of reverse thermal gelation, i.e., they are liquid at refrigerated temperatures (4-5° C.), but gel upon warming to room temperature. The gelation is reversible upon cooling.

At low temperatures in aqueous solutions, a hydration layer surrounds PF-127 molecules. When the temperature is raised, the hydrophilic chains of the copolymer become desolved as a result of the breakage of the hydrogen bonds that had been formed between the solvent and these chains. This phenomenon favors hydrophobic interactions among the polyoxypropylene domains and leads to gel formation. Because of the dehydration process, the hydroxyl groups become more accessible. A liquid micellar phase is stable at low temperatures but transforms into the cubic structure by increasing the temperature. At higher temperatures, a phase of hexagonal packed cylinders is formed, as shown in FIG. 2.



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Reverse thermal gelation and low toxicity have been the basis of research into the use of PF-127 as a possible drug delivery system in humans.

In a non-limiting example of DTCx materials in the context of the present invention, the hydrophilic character of the composition is an extremely important characteristic: It allows the polymer composition to gradually dissolve in the urine after the drug has been essentially released and the therapeutic session has been concluded without leaving foreign polymer composition residues inside the bladder.

The present invention's DTCx materials use a combination of polymers and drugs to obtain sustained release. Some of these materials have Reverse Thermal Gelation (RTG) property, thus can be injected as a free-flowing, low-viscosity liquid at low temperatures and form a gel upon exposure to body temperature. The DTCx materials present excellent rheology properties, high bio-adhesive capabilities in their gel state and high therapeutic efficacy. The present invention's DTCx materials soften in watery environment, such as exists in the bladder and will eventually dissolve. If needed, cooling the material inside the bladder with cold saline intravesical instillation will liquidize a DTCx material and wash it out of the bladder.

Materials to be utilized in the present application require a number of conditions to be fulfilled as follows:

- i. Sustained release of API. The materials can be tailored to release APIs for a pre-designed duration and according to a pre-designed profile.
- ii. Ability to insert material and coat through small orifices. Introducing DTCx materials into internal cavities requires good flow characteristics of the materials during insertion. One of the ways to get that capability is by using materials that act as 'plasticizer'—helping the material flow without significantly changing its viscosity and other rheology characteristics.
- iii. Adhesion and solidifying to internal surfaces for essentially pre-determined durations.

Some DTCx materials use polymers that have lower viscosities at low temperatures and gelate to high viscosities at body temperature. The gelling from low viscosity to high viscosity occurs at a specific temperature and produces mechanical tightening forces that enhance adhesiveness of the material to the tissue.

The gelation temperature (gel point) is an important system parameter in the design of the insertion, spreading and adhesiveness system. The liquid DTCx material that enters the bladder has to be fixed and adhered to the bladder wall fast enough to prevent it from flowing under gravitational forces toward the lowest point in the bladder before it is fixated. In a non-limiting example, the specific formulation of the DTCx may contain NaCl (table salt) that can lower the gelation temperature and help in controlling the instillation process.

The determination of gel point is important both because of the fact that the gel's performance when applied in the body heavily depends on such parameter as well as due to the fact that it reflects the precise composition of the substance, thus constituting an important QC parameter to be measured in both R&D and production settings.

The determination of gel point for the above admixtures is essential since it is desirable that, in the context of the present invention, the gel point will not drop dramatically given that the lower the gelling temperature, the more difficult will be to inject the composition through a catheter into the body cavity.

Care should be taken concerning the active drugs that are used: In some cases, such as in Mitomycin C that is

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manufactured and distributed by Kyowa Ltd., salts are added to the drug (for volume complementation) and these salts change the viscosity—temperature dependence, so that the gelling point of the material is significantly lower. To avoid the lower gelling point, most DTCx materials use pure chemotherapy compounds, without added salts.

Flexibility to enable adherence through cycles of enlargement/reduction or flexing of muscles is an essential property of the material disclosed in the present invention. For example, the volume of the bladder when DTCx material is instilled is 100 ml and when it is naturally filled with urine—it can grow to 300 ml and even more. The present invention's DTCx materials are designed to withstand such extreme cycles of expansion and collapse.

A range of compounds may be utilized to formulate a composition that will render the required properties as described in this invention. Non-limiting example of specific compositions utilized in the present invention are stated below.

In preferred embodiments of the invention, the material comprises polymers and copolymers chosen from among the following: Polycarboxylic acids such as polyglycolic acid polylactic acid and polyacrylic acid; polyurethanes; polyesters such as poly(ethylene terephthalate); polyamides such as nylon; polyacrylonitriles; polyphosphazenes; polylactones such as polycaprolactone; polyanhydrides such as poly[bis(p-carboxyphenoxy)propane anhydride; polyethylene; polyvinyl chloride; ethylene vinyl acetate; Poloxamer block copolymers of the type PEGPPG-PEG; polyethylene oxide (polyethylene glycol); polypropyleneoxide (polypropylene glycol); polymethylacrylate; polysaccharides as dextrin, cyclodextrins, hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose, hydroxymethylcellulose, chitosan, polyvinyl alcohol and polyvinyl acetate; Polylactide (PLA) and Poly(Lactide-co-Glycolide) (PLGA); polymer microspheres; starch and modified starches; and cellulose polymers.

The medicament formulations according to the invention may comprise the active ingredient in dissolved, suspended and/or solid, amorphous or crystalline form. The active ingredient can be employed in various particle sizes, e.g. in unground, ground or in micronized form, to produce the admix/formulation/mixture according to the invention with controlled release of active ingredient.

The admix/formulation/mixture described above with controlled release of active ingredient are for example in the form of active ingredient-containing hydrogels. These diffusion-controlled systems may be completely diluted in the hydrogel admix/formulation/mixture or can be multiparticulate, i.e. they may consist of a large number of coated cores such as, for example, of microencapsulated APIs, where appropriate together with conventional excipients and carriers, as defined below for example, is applied and subsequently coated with a diffusion coating which may comprise plasticizers and other excipients. The diffusion-controlled systems according to the invention may additionally consist of homogeneous active ingredient-containing cores which are produced for example by granulation, rotor granulation, fluidized bed agglomeration, tableting, wet extrusion or melt extrusion, where appropriate with spheronization, and are coated with a diffusion coating which may comprise plasticizers and other excipients. In a preferred embodiment of this invention, the active ingredient-containing particles comprise excipients such as, for example, acids or buffer substances which modify the pH and thus contribute to reducing the dependence of the release of active ingredient on the pH of the release medium. In a further preferred

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embodiment of this invention, the diffusion-controlled membrane comprises excipients which, through their pH-dependent solubility, influence the permeability of the membrane at different pH values and thus help to minimize the pH-dependence of the release of active ingredient.

The adhesive and thickening compounds preferably used in the production of coated neutral pellets (e.g. consisting of sucrose, microcrystalline cellulose, citric acid) are polycarbophil (polymer of acrylic acid crosslinked with divinyl glycol), hydroxypropylmethylcellulose (HPMC) and polyvinylpyrrolidone (PVP). It is likewise possible to employ other naturally, synthetic or partially synthetic polymers such as, for example methylcellulose (MC), hydroxypropylcellulose (HPC), other hydroxyalkylcelluloses and hydroxyalkylmethylcelluloses, carboxy-methylcelluloses and salts thereof, polyacrylic acids, polymethacrylates, gelatin, starch or starch derivatives, as well as gums like guar gum and xanthan gum.

Bonding agents employed for the production of active ingredient-containing microcapsules are for example polycarbophil, cellulose, microcrystalline cellulose, cellulose derivatives such as, for example, HMPC, HPC and low-substituted hydroxypropylcellulose (L-HPC), dicalcium phosphate, lactose, PVP and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPM-CAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides (e.g. alginic acid, alginates, galactomannans) waxes, fats and fatty acid derivatives.

pH-modifying substances such as, for example, acids, bases and buffer substances are incorporated into the active ingredient-containing core. Addition of these substances makes it possible to reduce markedly the pH-dependence of the release of the APIs. Examples of suitable excipients which modify the pH in the active ingredient-containing cores are: adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, toluenesulphonic acid, trometamol, tartaric acid. Citric acid, succinic acid, tartaric acid, potassium hydrogen tartrate are preferably employed.

Particularly suitable for producing the diffusion coating are ethylcelluloses and polymethacrylates such as, for example, EUDRAGIT® NE, EUDRAGIT® RS and RL. However, other materials such as, for example, cellulose acetate and cellulose acetate butyrate can also be employed as film-forming diffusion-controlling polymers.

Examples of plasticizers used are citric acid derivatives (e.g. triethyl citrate, tributyl citrate, acetyl triethyl citrate), phthalic acid derivatives (e.g. dimethyl phthalate, diethyl phthalate, dibutyl phthalate), benzoic acid and benzoic esters, other aromatic carboxylic esters (e.g. trimellithic esters), aliphatic dicarboxylic esters (e.g. dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters), glycerol monoacetate, glycerol diacetate or glycerol triacetate, polyols (e.g. glycerol, 1,2-propanediol, polyethylene glycol of varying chain length), fatty acids and derivatives (e.g. glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol) and fatty acid alcohols (e.g. cetyl alcohol, cetylstearyl alcohol). The nature and amount of the plasticizer are chosen so that the above-defined release according to the invention and the necessary stability of the medicinal forms is achieved. The proportion

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of the plasticizer is from 0 to 50%, preferably 0 to 35%, particularly preferably 0 to 25% based on the mass of the hydrogel composition.

The release rate according to the invention is controlled by the gel composition. Certain components may increase the permeability of the admix/formulation/mixture including water-soluble polymers such as, for example, polyethylene glycols, PVP, PVA, HPMC, HPC, hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans or other soluble substances such as, for example, urea, salts (sodium chloride, potassium chloride, ammonium chloride, etc.), sugars (sucrose, lactose, glucose, fructose, maltose etc.) and sugar alcohols (mannitol, sorbitol, xylitol, lactitol, etc.). Based on the mass of the hydrogel, from 0 to 50%, preferably 0 to 35%, particularly preferably 0 to 20%, increasing permeability components may be employed.

A further aspect of the present invention are coated admix/formulation/mixture which comprise one or more swellable excipients which, on penetration of liquid through the membrane, swell greatly and, through the swelling and volume expansion, cause the coating to split. The splitting of the coating makes it possible for the medicinal substance to be released from the admix/formulation/mixture, usually in pulsatile form. Swellable excipients which these formulations may comprise are, for example, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl starch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC). Examples of suitable coating materials are cellulose acetate, ethylcellulose and polymethacrylates.

The described diffusion-controlled or pulsatile formulations can be employed directly and unmodified as medicinal form. However, they may also be further processed, where appropriate with addition of excipients, to the final admix/formulation/mixture. In order to achieve a desired release profile it is also possible to combine different coated formulations in one medicinal form, and administration of an initial dose can take place for example by combination with rapid-release formulation particles, e.g. uncoated pellets, granules or powder.

In a further embodiment of the admix/formulation/mixture according to the invention with controlled release there is use of formulations which include the active ingredient in a admix/formulation/mixture. These group of admixes/formulations/mixtures release the active ingredient by diffusion and/or erosion.

The mass ratio of active ingredient to the total mass of the admix/formulation/mixture in these novel formulations is in the range from 1:1 to 1:1000, preferably in the range from 1:2 to 1:100.

Admixes/formulations/mixtures which can be employed are water-soluble, water-swellaable or water-insoluble substances. The novel formulations preferably comprise one or more water-swellaable polymers.

Preference is additionally given to medicinal preparations in the context of this invention which comprise water-soluble, hydrogel-forming polymers, these polymers having a nominal viscosity of at least 0.015 Pa s, preferably at least 0.050 Pa s (measured as 2% strength aqueous solution at 20° C.).

A preferred family of candidates to be utilized as a basis for obtaining said hydrogel is group of tri-block copolymers designated as PEG-PPG-PEG (PEG=Polyethylene glycol and PPG=Polypropylene glycol) and called Poloxamers, that produce reverse thermal gelaton compositions, i.e., with

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the characteristic that their viscosity increases with increasing temperature up to a point from which viscosity again decreases. In particular, Poloxamer 407 possesses a gelling temperature which is above 10° C. but below the human body temperature, i.e., 37° C. This characteristic may confer the ability of a composition containing the compound to be injected or infused in liquid state into a bodily inner cavity at a low temperature and, afterwards, as the composition warms, it becomes a gel, thus stabilizing upon the wall of the inner human cavity.

This characteristic has allowed PF-127 to be used as a carrier for most routes of administration including oral, topical, intranasal, vaginal, rectal, ocular and parenteral routes. In recent years PF-127 has attracted particular interest in the design of dermal and transdermal delivery systems, with a view to promoting, improving or retarding drug permeation through the skin, bearing in mind that for topical delivery systems, accumulation in the skin with minimal permeation is desired, while for systemic delivery, the opposite behavior is preferred. Poloxamer 407 (PF-127) is a nonionic surfactant composed of polyoxyethylene-polyoxypropylene copolymers in a concentration ranging from 20-30%. At low concentrations (10-4-10-5%) they form monomolecular micelles, but higher concentrations result in multimolecular aggregates consisting of a hydrophobic central core with their hydrophilic polyoxyethylene chains facing the external medium. Micellization occurs in dilute solutions of block copolymers in selected solvents above the critical micellar concentration, at a given temperature. At higher concentrations, above a critical gel concentration, the micelles can order into a lattice.

Aqueous solutions of poloxamers are stable in the presence of acids, alkalis, and metal ions. Commonly used poloxamers include the 88 (F-68 grade), 237 (F-87 grade), 338 (F-108 grade) and 407 (F-127 grade) types, which are freely soluble in water. The "F" designation refers to the flake form of the product. PF-127 has a good solubilizing capacity, low toxicity and is, therefore, considered a good medium for drug delivery systems. PF-127 is a commercially available polyoxyethylene-polyoxypropylene triblock copolymer of general formula E101 P56 E101, with an average molar mass of 13,000. It contains approximately 70% ethylene oxide, which accounts for its hydrophilicity. It is one of the series of poloxamer ABA block copolymers. As said above, PF-127 aqueous solutions of 20 to 30% w/w have the interesting characteristic: of reverse thermal gelation, i.e., they are liquid at refrigerated temperatures (4-5° C.), but gel upon warming to room temperature. The gelation is reversible upon cooling. This phenomenon, therefore, suggests that when poured onto the skin or injected into a body cavity, the gel preparation will form a solid artificial barrier and a sustained release depot. Furthermore, PF-127 has been reported to be the least toxic of commercially available copolymers.

Water-soluble or water-swellaable matrix-forming polymers preferably employed are hydroxy-propylmethylcelluloses (HPMC), hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses, methylcelluloses (MC), ethylcelluloses, other alkylcelluloses, hydroxy-alkylcelluloses and hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans such as, for example, guar and carob flour, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polymethacrylic acid derivatives, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin,

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gum arabic, tragacanth, gelatin, starch or starch derivatives and mixtures of these substances.

In this connection, the admix/formulation/mixture according to the invention should preferably comprise at least 0.1-2.0% of a hydroxypropylmethylcellulose type whose nominal viscosity (measured as 2% strength aqueous solution at 20° C.) is at least 0.015 Pa s, preferably at least 0.050 Pa s. HPMC types preferably used have a degree of substitution of methoxy groups of 16.5-30%, particularly preferably 19-30%, and a degree of substitution of hydroxypropoxy groups of 4-32%, particularly preferably 4-12%.

In a particularly preferred embodiment of this invention, substances which control the pH in the admix/formulation/mixture are incorporated into the admix/formulation/mixture. The addition of such pH-modifying excipients and/or the addition of substances which dissolve or are dissolved out of the admix/formulation/mixture as the pH increases, and thus increase the porosity or permeability of the admix/formulation/mixture and/or promote erosion of the admix/formulation/mixture, makes it possible to achieve a virtually pH-independent release for these preferred embodiments of the present invention.

Examples of suitable excipients which can be added to the admix/formulation/mixture according to the invention to achieve release which is as far as possible pH-independent are the following substances: adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, cellulose phthalates, in particular cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate, cellulose succinates, in particular cellulose acetate succinate and HPMCAS, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, polymethacrylates (e.g. EUDRAGIT® types), toluenesulphonic acid, trometamol, tartaric acid. Citric acid, succinic acid, tartaric acid, HPMCAS, and polymethacrylates (e.g. EUDRAGIT® L) are preferably employed. If these excipients are present in the admix/formulation/mixture according to the invention, they are typically added in a proportion of from 10 to 50% based on the total mass of the admix/formulation/mixture.

Examples of plasticizing excipients in the hydrogel formulation are propylene glycol, glycerol, triethylene glycol, butanediols, pentanols, such as pentaerythritol, hexanols, long-chain alcohols, polyethylene glycols, polypropylene glycols, polyethylene/propylene glycols, silicones, phthalic acid derivatives (e.g. dimethyl phthalate, diethyl phthalate, dibutyl phthalate), benzoic acid and benzoic esters, other aromatic carboxylic esters (e.g. trimellithic esters), citric acid derivatives (e.g. triethyl citrate, tributyl citrate, acetyl triethyl citrate), aliphatic dicarboxylic esters (e.g. dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters), glycerol monoacetate, glycerol diacetate or glycerol triacetate, fatty acids and derivatives (e.g. glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol), fatty acid alcohols (e.g. cetyl alcohol, cetylstearyl alcohol), sugars, sugar alcohols and sugar derivatives (e.g. erythritol, isomalt, lactitol, mannitol, maltitol, maltodextrin, xylitol). The concentration of plasticizers is normally from 0 to 30%, preferably from 0 to 20% based on the total mass of the gel.

Examples of suitable water-swellaable polymers which may be incorporated in the hydrogel are high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose,



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crosslinked sodium carboxymethyl starch, low-substituted hydroxypropylmethylcellulose (L-HPC), poly(hydroxyalkyl methacrylate), alginates and galactomannans and mixtures thereof.

The present invention further relates to the combination of formulations with different release properties, e.g. rapid-release and slow-release, in one medicinal form.

The present invention also includes the use of the novel pharmaceutical admix/formulation/mixture for producing medicaments which are intended for the treatment and/or prevention of disorders in humans.

The non-limiting examples presented below illustrate the versatility that is provided by the diverse compositions, that allows its engineering to render different release profiles, flow characteristics, instillation temperatures, coating layer thickness and additional features as required by the specific treatment to be applied upon an internal cavity.

DTCx materials are inserted into the essentially empty bladder using a catheter. The material is inserted at low temperature in the range of 10 c to 100 c, where the material viscosity is low enough to be able to flow freely into the bladder. As the liquid material flows into the bladder it is naturally heated by the body temperature and eventually it reaches that temperature. When the material temperature reaches the gelation temperature—it is passes from the liquid phase to viscous gel phase. The present invention's method is designed to ensure that material will cover essentially most of the surface of the bladder and that it will adhere to the bladder tissue at the point of contact.

In one preferred embodiment, a urinary catheter is used, such that incorporates a large balloon with a volume of 70 cc to 140 cc. The cold and liquid material is inserted into the bladder after the bladder was essentially emptied to minimize the amount of urine in the DTCx flow. The balloon is inflated to open the essentially collapsed bladder into an essentially symmetrical shape that is not less than a quarter of the volume of the bladder when it is filled with urine and reaches the volume that may cause urge to void (micturition).

In a preferred embodiment, the catheter system includes means to measure the momentary pressure that the balloon is applying on the bladder wall as indication for the physician to determine the level of inflating of the balloon. As a non-limited example, such means can measure the pressure of the liquid inside the balloon by connecting the supply tube into the balloon to a transparent column and reading the change in heights of liquid in that column as indication to the change in pressure on the bladder wall induced by inflating the balloon.

In a preferred embodiment, means are provided to make the flow out of the catheter exit from a hole positioned laterally close to the middle of the balloon.

In a preferred embodiment, means are provided to make the flow out of the catheter exit from the several holes set around the lateral middle of the balloon. The number of these exit holes can be between 2 and 4 holes. Means are provided to ensure that the catheter can be inserted into the urinary urethra in a known position, so that the position of each exit point is known. DTCx material is injected through the catheter in a number of doses that corresponds to the number of exit holes to control the overall distribution of the material around the balloon.

In a preferred embodiment each exit hole has a separate tube leading to it and each dose is injected into a separate tube, so that gelated material inside that tube does not disturb the flow of the next dose.

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In a preferred embodiment, the position of the patient is changed for each dose so that each dose is injected separately between the inflated balloon and downward toward the bladder wall—to utilize gravitation to assist material flow.

In a preferred embodiment means are provided to apply pressure on the material during its heating and gelation to help enhance its fixation and adhesion to the mucosal tissue of the bladder wall. In one preferred embodiment, the pressure is applied by the large balloon that is filled with liquid such as water or saline. In another—the balloon can be filled with a heavier liquid such as saturated salt water (26%, with typical density of 1.2 g/ml), or saturated solution of glucose in water.

In another preferred embodiment, the balloon contains magnetic material embedded into its design; in another non-limiting example the catheter balloon can contain a metal rod. In yet another non-limiting example the balloon can be inflated with ferromagnetic liquid such as ferrofluids, made of finely divided magnetite (a form of iron oxide that is ferromagnetic), an oily carrier and a surfactant like the composition produced by FerroTec, Inc—see <http://www.ferrotec.com/products/ferrofluid/>. In this example, the pressure is applied by an external magnet that is pulled to the magnet inside the balloon. The external magnet can be a stationary magnet and the patient can be positioned against it corresponding to the exit hole that will be injected through. In another arrangement, the magnet can be rotated around the patient. In another embodiment, the procedure can be administered inside a system such as an MRI unit that enables rotating the magnetic field electronically.

In a preferred embodiment, the instillation of doses can be repeated with a similar or different set of materials to achieve a second layer of coating with additional properties, such as blocking layer that will reduce the diffusion of material into the bladder and slow the natural degradation of the material into the urine in the bladder. In a non-limiting example the similar materials can be the polymer ingredient of the DTC material such as a mixture of one or more of PEG-400, PEG-800 or Poloxamer with distilled water. In a nonlimiting example, this mixture can be less viscous than the DTC material used for the first layer, thus having a slower diffusion rate and providing a barrier against release of drug into the bladder volume.

Following the instillation, the coating will release active ingredients with medical effect on the bladder disease, such as cancer fighting drugs that affect bladder cancer tumors. In parallel that coating will naturally and gradually dilute into the bladder urine and be expelled during urination.

In case it may become needed to speed this process of gradual dilution by external actions, in a preferred embodiment, the coating can be removed promptly by cooling the coating below its gelation temperature, thus significantly lowering its viscosity and speeding its dilution into the bladder urine. In a non-limited example, the cooling can be affected by flushing the bladder with a flow of cold liquid such as water or saline through a regular catheter into the bladder. Water and Saline will also help to melt water-based DTCx gels. In another preferred embodiment, the flow of cold liquid can be applied via a special catheter, which will enable a thin or focused jet of liquid that will exert pressure on a small part of the coating. In a preferred embodiment, the direction of this jet may be changed such that it can be activated on several areas of the bladder coating sequentially.

In another preferred embodiment, speeding the removal of the coating can be achieved by applying a chemical agent



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such as a solvent that can assist in the dissolution of the coating. The chemical agent can be chosen according to the formulation of the DTCx. As a non-limiting example, ethyl or isopropyl alcohol and DMSO (dimethyl sulfoxide) can be used to dissolve coatings that include lipophilic materials.

The versatility of the polymer composition and the ability to control its physicochemical properties may allow the incorporation and optimize sustained-release dosing of additional active ingredients that may be desired in a chemotherapy treatment, including the reduction of pain, avoidance of inflammation and other undesired effects. Thus, besides the active ingredients that serve as chemotherapy agents, other drugs can be incorporated in the gel composition, among them anesthetic drugs (e.g., lidocaine), coagulants (e.g., proconvertin) anticoagulants (like heparin), anti-inflammatory drugs (steroidal and non-steroidal) and others, according to the medical requirements for patients suffering of SBC utilizing the effect of gradual release of the diverse active components for an optimal treatment.

According to another embodiment of the present invention, other drugs can be incorporated in the gel composition. Such drugs can be administered topically and can belong to at least one of the following families: Antineoplastic drugs; Chemotherapeutic agents; Anti-infective agents (Antimicrobial drugs, Antiparasitic agents, Antivirals); Drugs acting on the blood and blood forming organs (Antihemorrhagics, Antithrombotic agents, antianemic drugs); Dermatologic drugs (antifungals, antiseptic); Genito-urinary system drugs; Gastrointestinal system (antiobesity, acid related disorders); Metabolism drugs; Anti-inflammatory product; Musculoskeletal system acting drugs; Neurological drugs; Respiratory drugs; Cardio-vascular drugs; Otolological drugs; Anti-infective drugs; Corticosteroids drugs; Analgesics and anesthetics drugs; Antiparasitics drugs or any combination thereof.

According to another embodiment of the present invention, other drugs can be incorporated in the gel composition. Such drugs can be selected from a group consisting of, Antibacterial s/Antibiotics, Antiinflammatories/Corticosteroids, Antineoplastics/Cytotoxics, Growth factors such as VEGF (Vascular Endothelial Growth Factor) and Inhibitory factors such as LIF (interleukin 6 class cytokine).

According to another embodiment of the present invention, at least one of the following is utilized in the admix/formulation/mixture: Poly (propylene oxide)—PPO, Poly (lactide-co-glycolic acid)—PLGA, Poly (N-isopropylacrylamide)—PNIPAM, Poly (propylene fumarate)—PPF, Poly (urethane)—PU, Poly (organophosphazene)—POP, Poloxamers of the type PEO-PPO-PEO (Poly (ethylene oxide), Poly (propylene oxide), Poly (ethylene oxide)) such as poloxamer 68, 88, 98, 108, 124, 127, 188, 237, 338 and 407, Stearic Acid, Poly (acrylic acid), Glyceryl Stearate, Cetearyl Alcohol, Sodium Stearoyl Lactylate, Hydroxy-Lenolin or any combination thereof.

According to another embodiment of the present invention the hydrogel/polymer composition may includes active pharmaceutical ingredients (APIs) that are expected to render a better therapeutic performance at lower risk levels. Specifically, the anticancerous drug mitomycin C (MMC) has been experimentally utilized in in vitro settings and applied on the internal bladder wall of animal specimens. The API is released in a controlled manner and the residence time inside the bladder is in the order of up to 24 hours instead of the accustomed 1-2 hours (until micturition).

According to another embodiment of the present invention the admix/formulation/mixture as provided above, can be used as biological glue so as to glue at least two tissues

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together. By adjusting the viscosity of the admix/formulation/mixture such biological glue can be provided.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein the weight of the balloon filled with a liquid denser than water is used for the application of the gel (utilizing its gravity).

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying force to said material further comprises a step of filling said catheter balloon with water and positioning the patient to utilize the gravitational forces directly toward the target tissue during the solidification of the material and cause optimal adhesion to that target tissue.

It is a further object of this invention to disclose such a method as defined in any of the above, wherein said step of applying gravitational force to said material further comprises a step of changing the position of the patient before applying partial doses of material to enable substantially full coating of the whole targeted internal cavity surface.

According to another embodiment, the material is used not only for coating internal cavities but rather coating organs selected from urinary bladder, mouth, nasal and paranasal sinus, gallbladder, esophagus, rectum, lungs, vagina, uterus, stomach, renal pelvis, pleura, abdomen, peritoneum, pelvis, liver, kidney, heart, intestine, brain, vertebral column, or any combination thereof.

In order better to illustrate how the invention may be put into practice, the following non-limiting examples of some of the embodiments of the invention are now provided.

#### EXAMPLE 1

The effectiveness of the present invention hydrogel composition drug delivery to the urinary tract is demonstrated by the following pre-clinical example. Two embodiments of reverse thermal gelation, mucoadhesive and flexible hydrogel mixed with MMC (Kyowa) at a concentration of 1 and 2 mg/ml were prepared as follows.

DTC1: The material comprised Pluronic F-127 Ethylene Oxide/Propylene Oxide Block Copolymer (27.0%); Polyethylene glycol, average MW=400 (PEG-400) (1.0%); Hydroxypropylmethyl cellulose (HPMC) (0.2%); with the remainder water for injection (71.8%) was mixed with MMC (Kyowa) at a concentration of 1 mg/ml.

DTC2: The material comprised Pluronic F-127 Ethylene Oxide/Propylene Oxide Block Copolymer (27.0%); Polyethylene glycol, average MW=400 (PEG-400) (1.0%); Hydroxypropylmethyl cellulose (HPMC) (0.2%); with the remainder water for injection (71.8%) was mixed with MMC (Kyowa) at a concentration of 2 mg/ml.

DTC1 and DTC2 were intravesically instilled in pigs. The MMC concentration in tissue was measured using HPLC and compared to intravesical instillation of 1 mg/ml MMC in water (standard treatment of Non-Muscle Invasive Bladder Cancer; Total MMC dosage of 40 mg). In addition, bladder condition following instillation and in-vivo gel dissolution rate were evaluated. Higher MMC tissue concentrations were obtained following DTC1 and DTC2 hydrogels treatments in comparison to the standard control treatment (MMC in water). Two hours following intravesical treatment of DTC1 the MMC concentration in urothelium tissue was 11 fold higher for the DTC1 in comparison to that of the control treatment (1 mg/ml MMC in water). The MMC concentration following intravesical treatment of DTC2 was 1.8 fold higher than that obtained for TC-3+1 mg/ml MMC. MMC tissue concentration 6 hr following instillation of DTC1 was 13 fold higher than that of the

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control treatment. Similar average MMC concentrations were obtained for DTC1 and DTC2. No damages to the urothelium contiguity, or bladder wall perforation were observed. The ureters and urethras were intact. No sign of ureter or urethral obstruction was observed. No clinical effects on animal's vital parameter were detected during the complete treatment duration. In addition, residues of MMC hydrogel were observed in the pig bladder 6 hrs following instillation, supporting release duration of more than 6 hr.

## EXAMPLE 2

One embodiment of the material disclosed in the present invention (DTC-1) that incorporates the active therapeutic agent Mitomycin C (MMC) was prepared as follows. The material comprised Pluronic F-127 Ethylene Oxide/Propylene Oxide Block Copolymer (27.0%); Polyethylene glycol, average MW=400 (PEG-400) (1.1%); Hydroxypropylmethyl cellulose (HPMC) (0.2%); MMC (0.1%); with the remainder (71.6%) double distilled water. DTC-1 has an instillation temperature of 30° C.; a sustained release duration of 12 hours; and a degradation time (until fully expelled from the body) of <24 hours.

## EXAMPLE 3

A second embodiment of the material disclosed in the present invention (DTC-1) that incorporates the active therapeutic agent Mitomycin C (MMC) was prepared as follows. The material comprised Pluronic F-127 (27.0%); PEG-400 (1.1%); HPMC (0.2%); MMC (0.2%); with the remainder (71.5%) double distilled water. DTC-2 has an instillation temperature of 50° C.; a sustained release duration of 16 hours; and a degradation time (until fully expelled from the body) of <24 hours.

## EXAMPLE 4

A third embodiment of the material disclosed in the present invention (DTC-3) that incorporates the active therapeutic agent Valrubicin was prepared as follows. The material comprised Pluronic F-127 (27.0%); PEG-400 (1.1%); HPMC (0.3%); Valrubicin (0.1%); with the remainder (71.6%) double distilled water. DTC-3 has an instillation temperature of 50° C.; a sustained release duration of 18 hours; and a degradation time (until fully expelled from the body) of 18 hours.

The increase in the amount of HPMC reduces the release rate from the carrier composition.

The dominant release parameter will be the composition dilution in the urine medium. The therapeutic agent is gradually released during the time until the composition is totally expelled from the body.

## EXAMPLE 5

A fourth embodiment of the material disclosed in the present invention (DTC-4), designed to have faster release and expulsion rates and which incorporates the active therapeutic agent MMC, was prepared as follows. The material comprised Pluronic F-127 (27.0%); PEG-400 (1.8%); HPMC (0.2%); MMC (0.1%); with the remainder (70.9%) double distilled water. DTC-4 has an instillation temperature of 30° C.; a sustained release duration of 10 hours; and a degradation time (until fully expelled from the body) of <16 hours.

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The decrease in the amount of PEG-400 increases the release rate from the carrier composition and the composition's dilution in the urine medium. In this case, drug is released more rapidly and the composition is totally expelled from the body within 16 hours.

## EXAMPLE 6

A fifth embodiment of the material disclosed in the present invention (DTC-5) that incorporates lidocaine was prepared as follows. The material comprised Pluronic F-127 (27.0%); PEG-400 (1.8%); HPMC (0.2%); Lidocaine 25 mg/10 ml composition (0.25%); with the remainder (70.75%) double distilled water. DTC-5 has an instillation temperature of 60° C.; a sustained release duration of 24 hours; and a degradation time (until fully expelled from the body) of 24 hours.

## EXAMPLE 7

A sixth embodiment of the material disclosed in the present invention (DTC-6) that incorporates the therapeutic agent MMC was prepared as follows. The material comprised Pluronic F-127 (27.0%); PEG-400 (1.1%); HPMC (0.2%); MMC (0.25%); with the remainder (71.35%) double distilled water. DTC-6 has an instillation temperature of 30° C.; a sustained release duration of 18 hours; and a degradation time (until fully expelled from the body) of 24 hours.

## EXAMPLE 8

A seventh embodiment of the material disclosed in the present invention (DTC-7) that incorporates the therapeutic agent Gemcitabine HCl was prepared as follows. The material comprised Pluronic F-127 (25.0%); HPMC (0.2%); Gemcitabine HCl 25 mg/10 ml composition (0.25%); with the remainder (74. %) double distilled water. DTC-7 has an instillation temperature of 20° C.; a sustained release duration of 12 hours; and a degradation time (until fully expelled from the body) of <18 hours.

It should be clarified that the above compositions refer to the use of chemically pure drugs. Commercially, some of the drugs are provided as admixtures of the active ingredient and other non-active compounds. For example, MMC is provided commercially in ampoules that contain 0.1 mg MMC and 240 mg sodium chloride, which provide an isotonic solution when dissolved in 10 ml double distilled water. The presence of salts as sodium chloride in the final material may have a considerable effect in the composition's physicochemical properties, among them and not limited to viscosity and gelation temperature, which are critical in the application method. These filler materials must be considered when formulating the different compositions, which should be adapted to the actual formulation of the active ingredient and its excipients.

## EXAMPLE 9

An in-vitro study was performed to evaluate the efficacy of DTCx materials as cytotoxic agents in the urinary bladder. A carcinoma cell line was treated with MMC incorporated into the material disclosed in the present invention, and the results the treatment were compared to treatment with MMC dissolved in saline. Viability was assessed by MTT assay which tests mitochondrial function.

Cell lines of human bladder cancer were grown in RPMI 1640 medium, supplemented with FBS, 100 U/ml penicillin

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and 100 mg/ml streptomycin. At Day 1 cells were seeded in 24-well plates at a MMC concentration of  $1 \times 10^4$  (four replicates for each concentration, 1 plate for each analysis time). The cells were then exposed for 24 hours to DTC-2; in separate experiments, DTC-2 samples that contained 0.05, 0.1, 0.5 or 1  $\mu\text{g/ml}$  MMC (Kyowa, Hakko Kogyo Co. Ltd.) were used. After 2 hours of incubation, medium was replaced with fresh medium for all plates. The plates were tested by taking out the medium and adding fresh medium containing MTT reagent. All other plates were returned to the incubator for incubation of 24, 72, 120 and 144 h. MTT assays were used to assess toxicity at all time points. The proportion of living cells was calculated by comparison to the control vehicle.

A microplate reader (EL 312e: Bio-Tek Instruments, Winooski Vt.) was used to evaluate the presence of LDH as a color development measured by absorbance spectroscopy at 450 nm. Background optical density (OD) was subtracted from the OD readings of all samples. Cell viability was calculated by dividing the mean OD absorbance values of the treated wells by the mean OD absorbance of the control wells. All samples were tested in triplicate.

Reference is now made to FIG. 3, which shows graphs of cell viability as a function of time for various experiments. These results clearly demonstrate MMC cytotoxicity when different MMC concentrations are used in saline and in TC-2 respectively.

These studies clearly demonstrate that a dramatic effect may be observed in the case of 0.1  $\mu\text{g/ml}$  (see FIG. 3A) where the difference between the effect of the DTC-2 hydrogel and that of the MMC-saline solution is most pronounced. For MMC-saline solution, there is practically no cell-kill, while with DTC-2 the cell-kill effect reaches 60%.

A direct relationship was demonstrated between MMC time of exposure and cytotoxicity. As seen in the graphs, in practically all cases the general trend is that the cytotoxicity increases as exposure time increases.

A direct relationship was also demonstrated between MMC concentration and cytotoxicity. Comparing the graphs obtained for different concentrations shows a higher cytotoxicity effect with the increase of concentration.

Thus, higher concentrations of MMC and longer exposure time contribute significantly to a higher cytotoxicity of MMC. When exposure time was increased from 2 hours to 24 hours, a cell kill level was achieved with less than one third of the MMC dose used for two hours exposure.

MMC concentrations in intravesical instillations have been evaluated in many different studies. Current treatment concentration is the highest that can be tolerated by the patient. Our results demonstrate that a further improvement in MMC efficacy can be gained by increasing the exposure time to MMC even at lower MMC concentrations.

#### EXAMPLE 10

The inventors of the present invention conducted a pre-clinical trial with sick female mice model testing the DTCx material (TC-1 polymer and Gemzar chemotherapy) on a MBT-2 disease model. These tumors are extremely aggressive and resistant to chemotherapy therefore somewhat differ from human superficial bladder cancer. In this study, treatment was applied 14, 10, and 3 days following cell implantation. Each group was divided into a DTCx material arm and a standard instillation arm consisting of Gemzar in saline, which served as control group. The results showed that the procedure was safe (indeed, with low mortality) and

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efficient, that is, consistent lower weights of cancerous bladder in the DTCx arm were obtained as compared to the control arm.

Large animal safety and efficacy studies were conducted on female pigs. The results demonstrated excellent control and no catheter-related or method-related adverse events.

The safety of the present invention's material and procedure by comparing the outcome of one week follow-up of animals following DTC-2 instillation to standard MMC instillation—seeking short & medium term adverse events (urinary retention, urethral obstruction, toxicity—both local and systemic).

Comparison of MMC concentrations in bladder tissue at 12 hours following instillation versus standard 2-hour instillation has demonstrated significantly higher MMC concentration in the bladder tissue for the procedure of the present invention, demonstrating the improved efficacy of the material and method disclosed in the present invention relative to methods known in the art for applying MMC to bladder tissue.

#### EXAMPLE 11

Studies performed by the inventors demonstrate that controlled release of the drug can be obtained which considerably prolong the actual contact between the bladder wall and the drug. This slow-release effect, which can take between 16 and 24 hours, dramatically increases such contact time and thus the continuous therapeutic effect of the drug upon the cancerous tissue. This effect, in tandem with the creation of an effective, stable coating upon the bladder wall, is expected to render a superior therapeutic effect in the treatment of bladder cancer.

In vitro studies performed by the inventors showed a gradual release of the drug embedded in the polymer composition in conditions similar to those of a human bladder (37° C., urine medium). The drug was gradually released throughout the tests over the course of 12-24 hours.

Further in vitro studies performed by the inventors show a gradual release of the drug embedded in the polymer composition in conditions similar to those of a human bladder (37° C., urine medium) when instead of continuously exposing the polymer composition to one portion of urine, such urine is changed every two hours and fresh portions replace the older ones during 24 hours. It was again found that the drug was gradually released throughout the tests during 16-24 hours.

A parallel set of in-vitro release experiments were performed using membraneless dissolution model: The hydrogel was loaded with the tested drug, layered in a glass containers, and equilibrated in the experimental temperature until homogenous gel layer was formed. acceptor solution was discarded every hour and replaced by a fresh solution. Drug concentration in acceptor solution was measured spectrophotometrically, gel dissolution was determined gravimetrically. Two examples are provided here.

- a. Reverse thermal gelation hydrogel composed of Pluronic F-127 Ethylene Oxide/Propylene Oxide Block Copolymer (27.0%); Polyethylene glycol, average MW=400 (PEG-400) (1.0%); Hydroxypropylmethyl cellulose (HPMC) (0.2%); and the remainder water for injection (71.8%) was loaded with at a concentration of 10 mg/ml and 20 mg/ml Lidocaine hydrochloride.

The in vitro release of Lidocaine hydrochloride (10 and 20 mg/ml) from the hydrogel formulation enclosed above is shown in FIG. 7. The released amount of Lidocaine hydrochloride was twofold higher for hydrogel loaded with 20



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mg/ml Lidocaine hydrochloride in comparison to the hydrogel loaded with 10 mg/ml Lidocaine hydrochloride formulation. In addition, higher amount of Lidocaine hydrochloride was released from both formulations to the acceptor solution in the first testing time point (1 hr). The amount of Lidocaine hydrochloride released in the following time points was relatively constant.

- b. Reverse thermal gelation hydrogel composed of Pluronic F-127 (20.0%); Pluronic F-68 (10.0%) Polyethylene glycol, average MW=400 (PEG-400) (1.0%); carboxymethyl cellulose sodium (CMC) (0.4%); and the remainder water for injection (68.8%) was loaded with at a concentration of 1 mg/ml cephalixin.

The in vitro release of cephalixin (1 mg/ml) from the hydrogel formulation enclosed above is shown in FIG. 7. The results demonstrate constant release of cephalixin at 3-6 hrs.

## EXAMPLE 12

Studies were performed on the adhesiveness of the material of the present invention to mucosal tissue. Remarkable, unexpected results were obtained.

Adhesiveness was measured by the "rolling ball" method according to the ASTM D-3121-94 and PTSC-6 standard methods. In these experiments, the adhesiveness of the material disclosed in the present invention was compared to the adhesiveness of compositions disclosed in U.S. Pat. Nos. 6,207,180; 6,894,071; and U.S. Pat. Appl. US2006/0127210. The results indicate that the material is potentially suitable for use as a drug carrier for the treatment of bladder cancer. The results are summarized in Table 2 and show a difference of at least 20 times in adhesive power.

TABLE 2

Composition	Test 1 Result (cm)	Test 2 Result (cm)
U.S. Pat. No. 6,207,180	32	20
U.S. Pat. No. 6,894,017	>45	>28
U.S. patent application 2006/0127420	>45	>28
present invention	1.0	1.6

## EXAMPLE 13

A second comparative study was performed in which the adhesiveness of the material of the present invention to biological material was compared with those of the three compositions cited in the previous example. The tests were performed according to ASTM standard D-2256-03, which determines adhesiveness by measuring peel strength. Adhesive properties were assessed applying equal amounts of the four compositions to biological tissues. Different types of loads were subjected to the samples, in order to mimic conditions occurring during in vivo applications. To standardize the test results, with respect to the multiplicity of applications and of tissues treated, pig bladder tissue was used as the unique substrate. The results are summarized in Table 3.

TABLE 3

Composition	Adhesiveness (N/cm <sup>2</sup> )
U.S. Pat. No. 6,207,180	0.068
U.S. Pat. No. 6,894,017	0.047

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TABLE 3-continued

Composition	Adhesiveness (N/cm <sup>2</sup> )
U.S. patent application 2006/0127420	0.090
present invention	1.77

These results demonstrate that the material of the present invention is at least 20 times more adhesive to biological tissue than the materials known in the prior art.

## EXAMPLE 14

A second set of in vitro tests of the bioadhesive properties of the material disclosed herein was performed. These tests were performed on fresh female swine bladder using a TAXT2 texture analyzer according to the following protocol.

A tissue specimen was placed on a foam tape mounted onto the cylindrical support of the instrument (2 cm diameter and 4 cm length) and secured with a string. The whole support was then positioned at the top of the measuring system and held in place by a clamp. A given weight of hydrogel (for example, 0.5 g) was evenly poured onto another support of similar dimensions. The support was then affixed on the lower probe of the instrument. The two supports were aligned to ensure that the gel comes into direct contact with the surface of the swine tissue when the upper support is lowered. Measurements were performed at 25° C.

Before measurement, 100 µl of simulated urine fluid was evenly spread on the surface of the tissue. The upper support was then lowered at a speed of 0.5 mm/s to contact with the gel at a force of 1 N for a contact time of 10 s. It was then withdrawn at a rate of 1.0 mm/s to a distance of 10 mm. An acquisition rate of 200 points/s was chosen for the analysis. Data collection and calculation can be performed using the XTRA Dimension software package of the instrument. The work of adhesion and peak detachment force were used to evaluate the bioadhesive strength of the films. The work of adhesion is calculated from the area under the force-distance curve, and the peak detachment force is taken as the maximum force needed for detaching the film from the tissue. All measurements were performed in triplicate. The results are summarized in Table 4.

TABLE 4

Formulation	Pluronic F127	HPMC	PEG 400	Double Distilled Water	Work of Adhesion (mJ)	of Peak Detachment Force (N)
A	25.0%	0.1%	0.5%	balance	0.51	3.34
B	27.0%	0.1%	1.0%	"	0.73	4.43
C	27.0%	0.2%	1.0%	"	1.13	6.35

A marked increase in the bioadhesion strength was observed with an increase in HPMC content.

## EXAMPLE 15

Gel point measurements were made for a number of embodiments of the material herein disclosed. The general procedure for the measurements was as follows. First, 50 ml of the material was poured into a 100-ml glass container. A TEFLON-coated magnet of 2-2.5 cm length was then placed in the container. A thermocouple was then inserted into the bulk of the hydrogel. The container was placed in an ice bath



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on a magnetic stirrer plate. After the temperature of hydrogel dropped to 5° C., the ice bath was removed from the magnetic stirrer and the glass container containing the hydrogel was placed directly on top of the magnetic stirrer plate. The magnetic stirrer was then turned on and run at medium speed (120 rpm). The temperature was allowed to rise gradually (~1° C./min) to room temperature. The gel point for a particular measurement was recorded as the temperature at which the magnet stopped rotating. For each sample, the entire procedure was performed twice, and the gel point determined as the average of the two measurements.

The gel point was measured for three different embodiments of the material disclosed herein. The results of the measurements are summarized in Table 5.

TABLE 5

Formulation	Pluronic F127	HPMC	PEG 400	Double Distilled Water	Gel Point (° C.)
A	25.0%	0.1%	0.5%	balance	16.5
B	27.0%	0.1%	1.0%	"	14.1
C	27.0%	0.2%	1.0%	"	11.9

A further set of tests was performed in which MMC was incorporated into the material at a typical dosage concentration in order to determine the effect of the MMC (and its accompanying excipient) on the gel point of the final composition. Formulation D includes pure MMC; formulation E includes commercially obtainable MMC that includes 2 parts mannitol per 1 part MMC (for example, Boehringer Mannheim) and Formulation F includes 24 parts of sodium chloride per 1 part MMC (for example, Kyowa). The results are summarized in Table 6.

TABLE 6

Formulation	Pluronic F127	HPMC	PEG 400	MMC	NaCl	Mannitol	Distilled Water	Point (° C.)
D	27.0%	0.2%	1.0%	0.1%	0	0	balance	11.8
E	27.0%	0.2%	1.0%	0.1%	0	0.2%	"	11.5
F	27.0%	0.2%	1.0%	0.1%	2.4%	0	"	5.1

As can be seen, incorporation of NaCl into the commercial MMC significantly lowers the gel point while mannitol does not affect the gel point very much. The major drop in gel point produced by NaCl as compared to that of mannitol can be explained by (a) the fact that the concentration of NaCl is significantly larger and (b) NaCl is an inorganic salt, thus releasing a number of moles of ions that is twice the number of moles of the original NaCl. The drop in gel point due to the addition of MMC itself is insignificant for practical purposes.

In addition to the gelation point of the reverse thermal gelation hydrogel its viscosity as a function of temperature is an important feature that determines the hydrogel's behavior and ability to perform properly. Therefore the rheological properties of formulation candidates were studied. The viscosity vs temperature curves and values of Tg (gelling temperature) for each formulation were determined by RV DV III Brookfield rheometer and DVII LV viscometer. The temperature at which a sharp increase in viscosity was obtained was determined as Tg. The viscosity measurement of the solid state of the gel (after complete solidification) was out of the range of the used rheometer and viscometer.

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Reference is now made to FIG. 5, which presents a semi-logarithmic graph of viscosity as a function of temperature over a range of 5-35° C. for six different embodiments of reverse thermal hydrogels disclosed in the present invention composition for effective drug delivery (TCA, TCB, TCC, TCD, TCE, TCF), and Table 7, which presents the results of a sample gel point measurements.

TABLE 7

Formulation	Pluronic F127	Pluronic F68	HPMC	CMC	PEG-400	Gel Point
TCA	27.0%	—	0.2%	—	1.0%	15° C.
TCB	20.0%	—	0.2%	—	1.0%	22° C.
TCC	20.0%	10.0%	0.2%	—	1.0%	33° C.
TCD	25.0%	5.0%	0.2	—	1.0%	17° C.
TCE	20.0%	10.0%	—	0.4%	1.0%	—
TCF	20.0%	—	—	0.2%	1.0%	20° C.

This information is fundamentally important for the design and engineering of the hydrogel device since viscosity characteristics are critical in the gel flow through the catheter and spreading upon the bladder inner surface as it is injected by means of the catheter.

## EXAMPLE 16

One of the main features that determines the hydrogel's behavior and ability to perform properly is its viscosity as a function of temperature. Therefore the rheological properties of formulation candidates were studied, including viscosity as a function of temperature and determination of gelling temperature (Tg).

The viscosity vs temperature curves and values of Tg (gelling temperature) for each formulation were determined

by means of an AR 1000-N Rheolyst rheometer (TA Instruments). The determination of Tg was determined through the crossover of the G' (elastic modulus) and G'' (viscous modulus) curves (see graph below the curves for TC-A).

Reference is now made to FIG. 5A, which presents a semi-logarithmic graph of viscosity as a function of temperature over a range of 4-50° C. for four different embodiments of the material herein disclosed (TCA, TCB, TCC, TCD), and to FIG. 5B, which presents the results of a sample gel point measurements. The formulations of the four embodiments are summarized in Table 8.

TABLE 8

Formulation	Pluronic F127	HPMC	PEG-400	Gel Point
TCA	27.0%	0.2%	1.0%	11.9° C.
TCB	25.5%	0.2%	1.0%	14.5° C.
TCC	25.5%	0.15%	1.0%	14.8° C.
TCD	23.0%	0.15%	0.5%	22.3° C.

Interestingly, increase in viscosity with temperature in the low temperature range is approximately logarithmic. As can

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be seen in the graph, even minor modifications of the same basic formulation can produce substantial changes in the rheological behavior of the product.

For TC-A, the values of viscosity in the temperature range of interest are 16 Pa s at 10° C., which is the temperature at which the gel (which at that temperature is still in liquid form) is expected to be cooled before application upon the bladder wall; and 4,600 Pa s at 37° C., which is the gel's final temperature (body temperature). As explained below, the method utilized allowed the determination of the gel point as well.

This information is fundamentally important for the design and engineering of the catheter/hydrogel device since viscosity characteristics are critical in the gel flow through the catheter and spreading upon the bladder inner surface as it is injected by means of the catheter.

## EXAMPLE 17

According to another embodiment, the mixture of gels obtained, according to the present invention, adhere well to the inner surface of human cavities, by their inherent reverse thermal gelling properties. Furthermore, they release the drug in a controlled way and that they themselves (the gels) gradually degrade so that they are expelled from the body in up to 24 hrs.

The following are further examples of mixtures according to the present invention:

17.1—Vitamin gel for topical action provided, according to the following:

Vitamin (A, D or K) 0.05% w/w Lecithin	12%
PEG 800	1%
Isopropyl stearate	8%
Pluronic F-127	20%
Double distilled water (DDW)	to 100%

17.2—Paclitaxel gel for cancer treatment, according to the following:

Paclitaxel	0.1%
Pluronic F-127	10.0%
Isopropyl Palmitate	1.0%
Lecithin	0.8%
Sodium Acryloyldimethyl-Taurate Copolymer	1.2%
Sorbic Acid	1.0%
Potassium Sorbate	0.1%
DDW	to 100%

17.3—Oral anesthetic gel, according to the following:

Lidocaine	1.0%
Pluronic F-127	27%
Ethoxyl diglycol	10%
Lecithin	2.0%
Mint flavor	0.1%
DDW	to 100%

17.4—Anti-inflammatory composition, according to the following:

PEG-PLGA-PEG*	24.5%
HPMC	0.2%
PEG 400	0.5%

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Ibuprofen	0.2%
DDW	to 100%

\*Ethylene glycol-lactic acid-co-glycolic acid-ethylene glycol triblock copolymer

17.5—Antibacterial gel, according to the following:

PEG 400	1.5%
PEG 1200	12.0%
Polysorbate 60	6%
Pluronic F-127	22%
Polyvinyl pyrrolidone-iodine complex	5.5%
DDW	to 100%

17.6—MMC gel, according to the following

Pluronic F-127	20%
Carboxymethyl cellulose sodium	0.5%
PEG 400	1%
MMC	0.2%
In 50 mM Tris-HCL buffer pH = 8	to 100%

17.7—Botox gel, according to the following

Pluronic F-127	20%
Carboxymethyl cellulose sodium	0.4%
PEG 400	1%
Botox 5 U/gr	
In 50 mM buffer acetate pH = 5	to 100%

## EXAMPLE 18

The effect of PEG-400 concentration on the gelation temperature was tested. The gelation temperature was determined at the temperature at which a sharp increase in the viscosity was observed (viscosity at gelation >106 mPa s) in a Brookfield rheometer DV-III, spindle 52.

The results are summarized in Table 9.

TABLE 9

Formulation	HPMC	PEG 400	Pluronic F127	Gelation temperature (° C.)
a	0.2	1	27	15
b	0.2	10	27	6

## EXAMPLE 19

The effect of HPMC concentration on the gel viscosity was measured. Viscosity measurements were performed using a Brookfield rheometer DV-III, spindle 52, at 6° C., and represent the viscosity of the formulation in its liquid state. The results are summarized in Table 10.

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TABLE 10

Formulation	HPMC (% w/w)	PEG-400 (% w/w)	Pluronic F127 (% w/w)	Viscosity (mPa s)
1	0.2	1	27	223
2	0.5	1	27	357
3	1.5	1	27	603
4	0.2	1	20	96
5	0.5	1	20	431
6	1.5	1	20	5742

## EXAMPLE 20

A gel composition according to the present invention was used for delivery of Mitomycin C (MMC) to pig bladder. MMC was incorporated into a gel containing 0.2% (w/w) HPMC, 1% (w/w) PEG-400, 27% (w/w) Pluronic F127 in water. In one experiment, the MMC concentration in the gel was 1 mg/ml (total dosage 40 mg); in another, the MMC concentration was 2 mg/ml (total dosage 80 mg). In each case, as a control, MMC was delivered from a solution containing MMC in the same concentration as in the analogous gel. The experimental results are summarized in FIG. 6.

As can be seen in the figure, higher MMC tissue concentrations were obtained following application of MMC contained in a gel of the present invention than by using a solution of MMC. Two hours following intravesical treatment by gel containing 1 mg/ml MMC, the MMC concentration in the tissue was 11 times higher than in the control. The MMC concentration in the tissue following application of gel with 2 mg/ml was 1.8 times higher than that in the experiment in which the concentration was 1 mg/ml. Six hours following treatment by gel containing 2 mg/ml MMC, the tissue MMC concentration was 13 times higher than in the control.

## EXAMPLE 21

An additional example for the effective drug delivery to the urinary tract of the present invention composition was demonstrated by a preclinical study testing the delivery of botulinum toxin A (BoNT-A) to rats bladder induced with chronic cystitis.

The effect of BoNT-A mixed with one embodiment of the invented material DTC-4 on bladder cystitis was demonstrated in a rat model (Sprague-Dawley) by comparing the effect of intravesical administration of BoNT-A in saline and in gel. The BoNT-A gel formulation (DTC-4) tested included 20 U BoNT-A/ml gel composed of 27% Pluronic F127, 0.2% HPMC and 1% PEG-400 in water. Intravesical instillation of just DTC-4 and of saline with no botulinum toxin served as control groups. Chronic cystitis was induced by intraperitoneal injection of Cyclophosphamide (75 mg/kg was injected on day 1, 4 and 7). On day 2 PE-50 tubing was inserted into the rat bladder through the urethra. The bladder was emptied of urine and filled with DTC-4 or saline with and without BoNT-A (1 ml, 20 u/ml Allergan). On day 8 the animals were anesthetized and their bladders were examined by cystometrogram recording via PE-50 tube inserted into the bladder dome. After recovery the animals were gently restrained and the suprapubic catheter was connected to infusion pump (0.08 ml/min continuously) and pressure transducer for recording intravesical pressure and for saline infusion into the bladder to elicit repetitive voiding. The

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amplitude and the inter-contraction interval of reflex bladder contractions were recorded. Each tested groups included 2-4 rats.

The bladder contraction amplitude measured is shown in FIG. 4. The results demonstrate that following CYP administration the bladder contraction amplitude increased from 25-27 mmHg (contraction level for rat bladder with no hyperactivity) to about 42 mmHg. Following administration of BoNT-A in saline and in TC-3 gel to rats with induced chronic cystitis the contraction decreased to the baseline level amplitude of 30 mmHg and 24 mmHg, respectively. Better response was received for the BoNT-A in gel treatment demonstrating the activity of the BoNT-A in gel and efficacy of BoNT-A mixes with gel treatment.

Similar results were obtained for the measurements of bladder inter-contraction intervals summarized in FIG. 4. Following CYP administration the bladder inter-contraction intervals were shown to decrease from 4-5 min for rat administered with saline or gel to 2 min. Intravesical administration of BoNT-A in saline and in TC-3 gel to rats with induced chronic cystitis increased the inter-contraction intervals to about 4 min, close to the inter-contraction intervals for bladder with no hyperactivity. These results further support the activity of the BoNT-A in the gel and the efficacy of the BoNT-A mixes with gel treatment.

## EXAMPLE 22

In order for the hydrogel formulation to be suitable for drug delivery in the bladder it must comply with the natural physiological changes in volume and shape i.e expansion during urine accumulation and contraction during urine voiding. During its the physiological function the bladder expands to about 5 times its original size. This property is tested for each hydrogel composition in the manner described hereof:

The flexibility of one embodiment of the reverse thermal gelation hydrogel (DTC1) for drug delivery was tested in vitro using sheep bladder tissue. To investigate the effect of tissue tension/expansion on hydrogel coverage, DTC1 stained with methylene blue was layered on top of a the mucosal side of rectangle section of bladder tissue with an area of 3\*3 cm. Following hydrogel gelation the tissue was starched and expanded by 3 fold to each direction (horizontally and vertically). The received area was 9 fold larger than the initial surface tissue area. The hydrogel coverage of the tissue following tissue expansion was examined. The hydrogel was shown to follow the stretched tissue. No gel detachment was observed.

## EXAMPLE 23

An important feature that influences the hydrogel is its dissolution rate/erosion rate. Therefore dissolution properties of hydrogels disclosed in the present invention composition were studied.

The dissolution rate was determined using an in-vitro membrane free dissolution model at 37° C. In this model the gel is dissolved into the receptor medium (Dulbecco's phosphate buffer saline) which is carefully layered on top of a smooth and flat gel layer. The amount of gel dissolved is determined gravimetrically. After each sampling of the receptor medium it is carefully discarded and replaced by a fresh medium.

Reference is now made to FIG. 8, which presents the dissolution rate of six different hydrogels herein disclosed. The results demonstrate different dissolution rate of the

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various formulations tested. These various dissolution rates will determine the treatment duration following instillation of the drug loaded hydrogel. Hence, the reverse thermal gelation hydrogel composition for effective treatment of the urinary tract will be set based on the beneficial treatment duration for specific disease.

## EXAMPLE 24

A further embodiment of the material disclosed in the present invention (DTC-11) is utilized upon organ linings consisting of serous tissue that does not possess a mucosal layer, in particular pleural and peritoneal walls. A condition common in several lung and heart diseases is pleural effusion, when serous fluids, pus or chyle accumulate into the space between the visceral pleura and the parietal pleura layers surrounding the lungs—condition called also hydrothorax. Certain malignancies enlarge the space between pleura layers and cause excessive levels of fluids to accumulate and impair breathing. Standard treatments for pleural effusions is the insertion of intercostals drain, often accompanied by surgical pleurodesis—in which the two pleural surfaces are scarred to each other so that no fluid can accumulate between them. Surgical joining of the layers is not always successful, but it is permanent.

A material of the present invention can be administered into the pleura cavity to adhere to the pleura layers and provide both a mechanical bond and sustained release of drug for treatment of the underlying malignancy (e.g. Tetracycline antibiotic for bacterial infection, or NSAID such as Naproxen to treat fever and inflammation).

The pleura-hydrogel material is inserted into the pleura space via a catheter or trocar, as non-viscous liquid at a temperature that is below 20° C. and adheres to the surrounding tissue as it heats to body temperature. The material is designed to dissolve gradually into the pleura fluids over less than a week and both maintain mechanical support and release therapeutic agents during that whole period.

This procedure can replace the more invasive pleurodesis with the additional benefits of tissue damage reduction, the soothing effect of the hydrogel and improved healing due to the sustained release of anti-inflammatory agents.

The following exemplary formulation can be applied (DTC11):

PEG-PLGA-PEG*	24.5%
HPMC	0.1%
PEG 400	0.4%
DDW	to 100%

\*Ethylene glycol-lactic acid-co-glycolic acid-ethylene glycol triblock copolymer

Said composition adheres well to said walls providing an effective matrix for the transport and release of therapeutic active ingredients. In particular, the admixture can carry anti-inflammatory drugs to be applied in case of pleural or peritoneal inflammation.

## EXAMPLE 25

Fixation of organs and prevention of tissue adhesion in the abdomen during laparoscopy:

A material of the current invention can be introduced into the abdomen cavity and provide mechanical support to the target organs in the position that best fits the surgical procedure. The peritoneum-hydrogel material can be inserted into the peritoneum cavity via endoscope working

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channel, a catheter or trocar, as non-viscous liquid at a temperature that is below 15° C. and adhere to the surrounding tissue as it heats to body temperature. The material is designed to dissolve gradually into the pleura fluids over less than a week and both maintain mechanical support of the organs for several hours and release the drugs during a longer period.

Similar method, but with different materials can be used to prevent the adhesion of tissues between organs in the treated area, which may often occur during laparoscopic surgery.

The main advantages of this method are the combination of its ability to replace a more invasive procedure, the reduction of tissue damage, the soothing effect of the hydrogel and the enhanced healing effect of the sustained release of anti-inflammatory agents. A further advantage is the prevention of the need to remove the fixation surgically because of the natural degradation and expelling of the invented material from the treated area.

The following exemplary formulation can be applied (DTC-12):

PEG-PLGA-PEG*	24.5%
CMC	0.4%
PEG 400	0.4%
DDW	to 100%

## EXAMPLE 26

A binary API system (DTC-13 to DTC-16) was formulated which allowed a different release profile from the same gel structure. The relative release rate from the basic formulation was controlled by the addition of changing amounts of the surfactant sodium dodecyl sulfate (SDS), which affected the overall lipophilic/hydrophilic balance of the formulation. The APIs in question were mitomycin C (MMC) and lidocaine. The following table presents the composition of three basic formulations and the release time of 80% of each of the two APIs. From an applicative point of view, it is of much interest to obtain a relatively rapid release of lidocaine, which produces the local anesthetic effect upon the organ tissue to be treated, followed by a slow release of the MMC, that may allow a superior chemotherapeutic treatment of said organ.

TABLE 11

DTC-16	DTC-15	DTC-14	DTC-13	MATERIAL
27.0	27.0	27.0	27.0	Pluronic F127 (%)
0.2	0.2	0.2	0.2	HPMC (%)
1.0	1.0	1.0	1.0	PEG-400 (%)
0.2	0.1	0.05	0	SDS (%)
71.6	71.7	71.75	71.8	DDW (%)
0.1	0.1	0.1	0.1	MMC (%)
1.0	1.0	1.0	1.0	Lidocaine (%)
12	14	15	16	Release time 80% MMC (hrs)
10	60	120	180	Release time 80% Lidocaine (min)

The results shown in table 11 demonstrate that adding a small amount of SDS dramatically affects the release profile of the two drugs respectively. This exemplifies, without limiting, the possibilities of engineering the gel composition in a way that allows two or more different APIs to release from the gel matrix each at their own pace—according to the



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treatment needs. In the example above, it may be desirable, for example, that the soothing effect of the lidocaine be felt by the patient rapidly, just before the MMC commences its own activity, that may be painful, and thus a rapid release of the lidocaine may be desired while a slow release of the same may be unfelt and this ineffective. On the other hand, one can conceive other treatments where a lower but more prolonged anesthetic effect be required, and thus the formulation will change accordingly. The possibilities are limitless as presented by the non-limiting examples above.

We claim:

1. A thermoreversible hydrogel, comprising:
  - between 20% and 30% (w/w) of an ethylene oxide/propylene oxide triblock copolymer;
  - between 0.05% and 0.3% hydroxypropylmethylcellulose (HPMC);
  - between 0.4 and 2.5% polyethylene glycol 400 (PEG-400);
  - an effective amount of a therapeutic agent; and the balance water.
2. The thermoreversible hydrogel of claim 1, comprising:
  - between 0.1% and 0.3% hydroxypropylmethylcellulose (HPMC); and
  - between 0.4 and 1.8% polyethylene glycol 400 (PEG-400).
3. A thermoreversible hydrogel, comprising:
  - between 23% and 27% (w/w) of an ethylene oxide/propylene oxide triblock copolymer having a general formula E101 P56 E101;
  - between 0.1% and 0.2% hydroxypropylmethylcellulose (HPMC);
  - between 0.5% and 1% polyethylene glycol 400 (PEG-400); and the balance water.
4. The thermoreversible hydrogel of claim 1, further comprising at least one component selected from the group consisting of:
  - adhesive and thickening compounds;
  - at least one bonding agents selected from the group consisting of polycarbophil, cellulose, microcrystalline cellulose, low substituted hydroxypropylcellulose (L-HPC), dicalcium phosphate, lactose, polyvinylpyrrolidone (PVP) and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides, fats, fatty acids, and any combination thereof pH-modifying substances;
  - at least one diffusion coating selected from the group consisting of ethylcelluloses and polymethacrylates, cellulose acetate, cellulose acetate butyrate and any combination thereof;
  - plasticizers;
  - at least one substance selected from swellable excipients group consisting of polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl starch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC), cellulose acetate, ethylcellulose and polymethacrylates, high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium

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- carboxymethyl starch, poly(hydroxyalkyl methacrylate), alginates, galactomannans, and any combination thereof;
- at least one substance chosen from the group of water soluble polymers consisting of polyethylene glycols, PVP, PVA, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses (HEC), methylcellulose (MC), carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans urea, salts, sodium chloride, potassium chloride, ammonium chloride, sugars, sucrose, lactose, glucose, fructose, maltose, sugar alcohols, mannitol, sorbitol, xylitol, lactitol, and any combination thereof;
- at least one substance chosen from matrix-forming polymers group consisting of hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, alkylcelluloses, hydroxy-alkylcelluloses hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch, and any combination thereof.
- 5. The thermoreversible hydrogel of claim 4, wherein the adhesive and thickening compounds are selected from the group consisting of polycarbophil, crosslinked acrylic acid, divinyl glycol, polyvinylpyrrolidone (PVP), methylcellulose (MC), hydroxy-propylcellulose (HPC), other hydroxyalkylcelluloses, hydroxyalkylmethylcelluloses, carboxy-methylcelluloses and salts thereof, polyacrylic acids, polymethacrylates, gelatin, starch, as well as gums like guar gum and xanthan gum and any combination thereof.
- 6. The thermoreversible hydrogel of 18, wherein:
  - the pH-modifying substances are selected from the group consisting of acids, bases and buffer, adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, toluenesulphonic acid, trometamol, tartaric acid, and any combination thereof and,
  - the plasticizers are selected from the group consisting of citric acid, triethyl citrate, tributyl citrate, acetyl triethyl citrate; phthalic acid, dimethyl phthalate, diethyl phthalate, dibutyl phthalate; benzoic acid and benzoic esters, other aromatic carboxylic esters, trimellitic esters, aliphatic dicarboxylic esters, dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters, glycerol monoacetate; glycerol diacetate or glycerol triacetate, polyols, glycerol, 1,2-propanediol, polyethylene glycol of varying chain length, fatty acids, glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol, fatty acid alcohols, cetyl alcohol, cetylstearyl alcohol and any combination thereof.
- 7. The hydrogel of claim 1, further comprising at least one component selected from the group consisting of poly(propylene oxide) (PPO), poly(lactide-co-glycolic acid) (PLGA), poly(N-isopropylacrylamide) (PNIPAM), poly(propylene fumarate) (PPF), polyurethane (PU), poly(organophosphazene) (POP), Poloxamers of the type (poly(ethylene oxide)/poly(propylene oxide)/poly(ethylene oxide)) (PEO-PPO-PEO), stearic acid, poly(acrylic acid),

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glyceryl stearate, cetearyl alcohol, sodium stearoyl lactylate, hydroxy-lanolin, and any combination thereof.

8. The thermoreversible hydrogel of claim 1, comprising an active pharmaceutical ingredient selected from the group consisting of antineoplastic drugs; chemotherapeutic agents; anti-infective agents, antimicrobial drugs, antiparasitic agents, antivirals; drugs acting on the blood and blood forming organs, antihemorrhagics, antithrombotic agents, antianemia drugs, dermatologic drugs, antifungals, antiseptics, genito-urinary system drugs, gastrointestinal system drugs, antiobesity drugs, drugs for treating acid related disorders, metabolism drugs, anti-inflammatory product, musculoskeletal system acting drugs; neurological drugs, respiratory drugs, gene therapy, cardio-vascular drugs, otological drugs, corticosteroids, analgesic and anesthetic drugs, growth factors, vascular endothelial growth factor (VEGF), inhibitory factors, interleukin 6 class cytokine (LIF) and any combination thereof.

9. The thermoreversible hydrogel of claim 8 wherein the active pharmaceutical agent is selected from the group consisting of Mitomycin C, Deoxrubicin, Valrubicin, Gemcitabine, Thiotepa, Taxotere, Ethoglucid (Epodyl), Epirubicin, Pirarubicin, Apaziquone, Vicinium, Botulinum toxin, Fibrin, Lidocaine, Thrombin, Collagen, Naproxen and Ibuprofen.

10. A method for providing sustained-release topical treatment of a condition affecting an internal body cavity, comprising administering the hydrogel of claim 8 to the internal body cavity.

11. A method for providing sustained-release topical treatment of a condition affecting an internal body cavity, comprising administering the hydrogel of claim 9 to the internal body cavity.

12. The method of claim 10, wherein the internal body cavity is at least one selected from the group consisting of the urinary bladder, mouth, nasal and paranasal sinus, gall-bladder, esophagus, rectum, lungs, vagina, uterus, stomach, renal pelvis, pleura, abdomen, peritoneum, pelvis, liver, kidney, heart, intestine, brain, vertebral column, and any combination thereof.

13. The method of claim 11, wherein the internal body cavity is at least one selected from the group consisting of the urinary bladder, mouth, nasal and paranasal sinus, gall-bladder, esophagus, rectum, lungs, vagina, uterus, stomach, renal pelvis, pleura, abdomen, peritoneum, pelvis, liver, kidney, heart, intestine, brain, vertebral column, and any combination thereof.

14. The method of claim 10, wherein the hydrogel provides for parenteral administration of the active pharmaceutical ingredient.

15. A thermoreversible hydrogel, comprising:

between 20% and 30% (w/w) of an ethylene oxide/propylene oxide triblock copolymer;

between 0.05% and 0.3% hydroxypropylmethylcellulose (HPMC);

between 0.4 and 2.5% polyethylene glycol 400 (PEG-400);

an effective amount of a therapeutic agent selected from the group consisting of Mitomycin C, Deoxrubicin, Valrubicin, Gemcitabine, Thiotepa, Taxotere, Ethoglucid (Epodyl), Epirubicin, Pirarubicin, Apaziquone, Vicinium, Botulinum toxin, Fibrin, Lidocaine, Thrombin, Collagen, Naproxen and Ibuprofen; and the balance water.

16. The thermoreversible hydrogel of claim 15, comprising:

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between 0.1% and 0.3% hydroxypropylmethylcellulose (HPMC); and

between 0.4% and 1.8% polyethylene glycol 400 (PEG-400).

17. The thermoreversible hydrogel of claim 15, comprising:

between 23% and 27% (w/w) of an ethylene oxide/propylene oxide triblock copolymer having a general formula E101 P56 E101;

between 0.1% and 0.2% hydroxypropylmethylcellulose (HPMC);

between 0.5% and 1% polyethylene glycol 400 (PEG-400); and the balance water.

18. The thermoreversible hydrogel of claim 15, further comprising at least one component selected from the group consisting of:

adhesive and thickening compounds;

at least one bonding agents selected from the group consisting of polycarboxophil, cellulose, microcrystalline cellulose, low substituted hydroxypropylcellulose (L-HPC), dicalcium phosphate, lactose, polyvinylpyrrolidone (PVP) and sucrose, ethylcellulose, hydroxypropylmethylcellulose acetate succinate (HPMCAS), PVP, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, polyethylene oxide, polymethacrylates, polyvinyl alcohols (PVA), partially hydrolysed polyvinyl acetate (PVAc), polysaccharides, fats, fatty acids, and any combination thereof pH-modifying substances;

at least one diffusion coating selected from the group consisting of ethylcelluloses and polymethacrylates, cellulose acetate, cellulose acetate butyrate and any combination thereof;

plasticizers;

at least one substance selected from swellable excipients group consisting of polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl starch, polyethylene oxides, polymethacrylates, low-substituted hydroxypropylmethylcellulose (L-HPC), cellulose acetate, ethylcellulose and polymethacrylates, high-molecular weight polyethylene oxides, xanthan gum, copolymers of vinylpyrrolidone and vinyl acetate, polyvinylpyrrolidones, crospovidones, crosslinked sodium carboxymethylcellulose, crosslinked sodium carboxymethyl starch, poly(hydroxyalkyl methacrylate), alginates, galactomannans, and any combination thereof; at least one substance chosen from the group of water soluble polymers consisting of polyethylene glycols, PVP, PVA, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses (HEC), MC, carboxymethylcelluloses or their salts, dextrans, maltodextrins, cyclodextrins, dextrans urea, salts, sodium chloride, potassium chloride, ammonium chloride, sugars, sucrose, lactose, glucose, fructose, maltose, sugar alcohols, mannitol, sorbitol, xylitol, lactitol, and any combination thereof

at least one substance chosen from matrix-forming polymers group consisting of hydroxyethylmethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses methylcelluloses (MC), ethylcelluloses, alkylcelluloses, hydroxy-alkylcelluloses hydroxyalkylmethylcelluloses, sodium carboxymethylcelluloses (NaCMC), alginates, galactomannans, xanthans, polyethylene oxides, polyacrylic acids, polymethacrylic acids, polyvinyl alcohols (PVA), partially hydrolysed

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polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), agar, pectin, gum arabic, tragacanth, gelatin, starch, and any combination thereof.

19. The thermoreversible hydrogel of claim 15, wherein the adhesive and thickening compounds are selected from the group consisting of polycarbophil, crosslinked acrylic acid, divinyl glycol, polyvinylpyrrolidone (PVP), methylcellulose (MC), hydroxy-propylcellulose (HPC), other hydroxyalkylcelluloses, hydroxyalkylmethylcelluloses, carboxy-methylcelluloses and salts thereof, polyacrylic acids, polymethacrylates, gelatin, starch, as well as gums like guar gum and xanthan gum and any combination thereof.

20. The thermoreversible hydrogel of 22, wherein:

the pH-modifying substances are selected from the group consisting of acids, bases and buffer, adipic acid, malic acid, L-arginine, ascorbic acid, aspartic acid, benzenesulphonic acid, benzoic acid, succinic acid, citric acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, fumaric acid, gluconic acid, glucuronic acid, glutamic acid, potassium hydrogen tartrate, maleic acid, malonic acid, methanesulphonic acid, toluenesulphonic acid, trometamol, tartaric acid, and any combination thereof and, the plasticizers are selected from the group consisting of citric acid, triethyl citrate, tributyl citrate, acetyl triethyl citrate, phthalic acid, dimethyl phthalate, diethyl phthalate, dibutyl phthalate; benzoic acid and benzoic esters, other aromatic carboxylic esters, trimellithic esters, aliphatic dicarboxylic esters, dialkyl adipates, sebacic esters, in particular diethyl sebacate, tartaric esters, glycerol monoacetate, glycerol diacetate or glycerol triacetate, polyols, glycerol, 1,2-propanediol, polyethylene glycol of varying chain length, fatty acids, glycerol monostearates, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol, fatty acid alcohols, cetyl alcohol, cetylstearyl alcohol and any combination thereof.

21. The hydrogel of claim 15, further comprising at least one component selected from the group consisting of poly(propylene oxide) (PPO), poly(lactide-co-glycolic acid) (PLGA), poly(N-isopropylacrylamide) (PNIPAM), poly(propylene fumarate) (PPF), polyurethane (PU), poly(organophosphazene) (POP), Poloxamers of the type (poly(ethylene oxide)/poly(propylene oxide)/poly(ethylene oxide)) (PEO-PPO-PEO), stearic acid, poly(acrylic acid), glyceryl stearate, cetearyl alcohol, sodium stearoyl lactylate, hydroxy-lanolin, and any combination thereof.

22. The method of claim 11, wherein the hydrogel provides for parenteral administration of the active pharmaceutical ingredient.

23. The thermoreversible hydrogel of claim 1, wherein the therapeutic agent is mitomycin C, and having one or more of the following:

a viscosity of less than 5 P·s over a temperature range of 4° C.-12° C.;

a viscosity of greater than 10<sup>3</sup> Pa·s over at 37° C.;

a peel strength of 0.5-5.0 N<sup>-2</sup> tested using ASTM D2256-03 at 37° C.; and

a flexibility such that a 3 cm<sup>2</sup>×3 cm<sup>2</sup> section of bladder tissue layered with the thermoreversible hydrogel at

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room temperature can be stretched to 9 cm<sup>2</sup>×9 cm<sup>2</sup> without detachment of the thermoreversible hydrogel from the bladder tissue.

24. The thermoreversible hydrogel of claim 23, having two or more of the following:

a viscosity of less than 5 P·s over a temperature range of 4° C.-12° C.;

a viscosity of greater than 10<sup>3</sup> Pa·s over at 37° C.;

a peel strength of 0.5-5.0 N<sup>-2</sup> tested using ASTM D2256-03 at 37° C.; and

a flexibility such that a 3 cm<sup>2</sup>×3 cm<sup>2</sup> section of bladder tissue layered with the thermoreversible hydrogel at room temperature can be stretched to 9 cm<sup>2</sup>×9 cm<sup>2</sup> without detachment of the thermoreversible hydrogel from the bladder tissue.

25. The thermoreversible hydrogel of claim 23, having three or more of the following:

a viscosity of less than 5 P·s over a temperature range of 4° C.-12° C.;

a viscosity of greater than 10<sup>3</sup> Pa·s over at 37° C.;

a peel strength of 0.5-5.0 N<sup>-2</sup> tested using ASTM D2256-03 at 37° C.; and

a flexibility such that a 3 cm<sup>2</sup>×3 cm<sup>2</sup> section of bladder tissue layered with the thermoreversible hydrogel at room temperature can be stretched to 9 cm<sup>2</sup>×9 cm<sup>2</sup> without detachment of the thermoreversible hydrogel from the bladder tissue.

26. The thermoreversible hydrogel of claim 23, having the following:

a viscosity of less than 5 P·s over a temperature range of 4° C.-12° C.;

a viscosity of greater than 10<sup>3</sup> Pa·s over at 37° C.;

a peel strength of 0.5-5.0 N<sup>-2</sup> tested using ASTM D2256-03 at 37° C.; and

a flexibility such that a 3 cm<sup>2</sup>×3 cm<sup>2</sup> section of bladder tissue layered with the thermoreversible hydrogel at room temperature can be stretched to 9 cm<sup>2</sup>×9 cm<sup>2</sup> without detachment of the thermoreversible hydrogel from the bladder tissue.

27. The thermoreversible hydrogel of claim 1, wherein the therapeutic agent is mitomycin C, the ethylene oxide/propylene oxide triblock copolymer has the general formula E101 P56 E101, and the thermoreversible hydrogel completely degrades in less than 24 hours after administration to the bladder of a patient.

28. The thermoreversible hydrogel of claim 1, wherein the therapeutic agent is mitomycin C and the thermoreversible hydrogel has a viscosity of less than 200 Pa·s at a temperature ranging from 8° C. to 25° C., and greater than 3000 Pa·s at a range of 35° C. to 37° C.

29. The thermoreversible hydrogel of claim 28, wherein the mitomycin C is present in an amount which is therapeutically effective for treating superficial bladder cancer.

30. The thermoreversible hydrogel of claim 1, wherein the therapeutic agent is mitomycin C and after administration the therapeutic agent is continuously released for at least 16 hours.

\* \* \* \* \*

# EXHIBIT C



**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use JELMYTO safely and effectively. See full prescribing information for JELMYTO.

**JELMYTO® (mitomycin) for pyelocalyceal solution**

Initial U.S. Approval: 1974

**RECENT MAJOR CHANGES**

Dosage and Administration, Preparation and Handling (2.3) 09/2022

**INDICATIONS AND USAGE**

JELMYTO is an alkylating drug indicated for the treatment of adult patients with low-grade Upper Tract Urothelial Cancer (LG-UTUC). (1)

**DOSAGE AND ADMINISTRATION**

- JELMYTO is for pyelocalyceal use only and not for intravenous use, topical use, or oral administration. (2.1)
- Administer 1.3 g of sodium bicarbonate orally the evening prior to, the morning of, and 30 minutes prior to instillation procedure (total of 3.9 g). (2.1)
- The dose of JELMYTO to be instilled is 4 mg per mL via ureteral catheter or nephrostomy tube, with total instillation volume based on volumetric measurements using pyelography, not to exceed 15 mL (60 mg of mitomycin). (2.2)
- Instill JELMYTO once weekly for six weeks. For patients with a complete response 3 months after JELMYTO initiation, JELMYTO instillations may be administered once a month for a maximum of 11 additional instillations. (2.2)

**DOSAGE FORMS AND STRENGTHS**

For pyelocalyceal solution: A kit containing the following:

- Two 40 mg (each) single-dose vials of mitomycin for pyelocalyceal solution (3)

- One vial of 20 mL sterile hydrogel for reconstitution (3)

**CONTRAINDICATIONS**

- Perforation of the bladder or upper urinary tract. (4)

**WARNINGS AND PRECAUTIONS**

- Ureteric Obstruction: Ureteric obstruction may occur. Monitor patients for signs and symptoms of ureteric obstruction. Transient or long-term ureteral stents or alternative procedures may be required. Withhold or permanently discontinue JELMYTO based on the severity of the ureteric obstruction. (5.1)
- Bone Marrow Suppression: Thrombocytopenia and neutropenia may occur. Monitor blood counts. Withhold or permanently discontinue JELMYTO based on the severity. (5.2)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and to use effective contraception. (5.3, 8.1, 8.3)

**ADVERSE REACTIONS**

The most common adverse reactions ( $\geq 20\%$ ) are ureteric obstruction, flank pain, urinary tract infection, hematuria, abdominal pain, fatigue, renal dysfunction, nausea, dysuria, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UroGen Pharma at 1-855-987-6436 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**USE IN SPECIFIC POPULATIONS**

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2022

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\*Sections or subsections omitted from the full prescribing information are not listed

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

JELMYTO<sup>®</sup> is indicated for the treatment of adult patients with low-grade Upper Tract Urothelial Cancer (LG-UTUC).

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Important Administration Instructions

See the Instructions for Administration provided separately.

**JELMYTO is for pyelocalyceal use only.** JELMYTO is not for intravenous use, topical use, or oral administration. Prior to every instillation, instruct the patient to take 1.3 g of sodium bicarbonate orally the evening prior to, the morning of, and 30 minutes prior to the instillation procedure (total of 3.9 g).

General anesthesia, local anesthesia, sedation, prophylactic antibiotics and/or antihistamines may be used at the discretion of the treating urologist. If the patient is to be anesthetized, advise the patient not to take sodium bicarbonate within 30 minutes prior to the treatment.

Consider withholding diuretics one day prior to instillation until 4 hours post-instillation.

When instilling JELMYTO, the entire syringe must be emptied within one minute.

Advise patients that JELMYTO may discolor urine to a violet to blue color following the instillation procedure. Advise patients to avoid contact with urine for at least six hours post-instillation, to void urine sitting on a toilet, and to flush the toilet several times after use.

#### 2.2 Recommended Dosage

The dose of JELMYTO to be instilled is 4 mg per mL via ureteral catheter or a nephrostomy tube, with total instillation volume based on volumetric measurements using pyelography, not to exceed 15 mL (60 mg of mitomycin).

Instill JELMYTO once weekly for six weeks. For patients with a complete response 3 months after JELMYTO initiation, JELMYTO instillations may be administered once a month for a maximum of 11 additional instillations.

#### 2.3 Preparation and Handling

See the Instructions for Pharmacy for preparation provided separately.

JELMYTO is a hazardous drug. Follow applicable special handling and disposal procedures.<sup>1</sup>

JELMYTO must be prepared under chilled conditions. Once reconstituted, the admixture will have a concentration of 4 mg of mitomycin per mL and will appear as a viscous liquid for instillation. Reconstituted JELMYTO has reverse thermal properties with a gelation point of approximately 19°C (66°F). Reconstituted JELMYTO should be instilled as soon as possible after reconstitution. Store reconstituted JELMYTO at 20°C to 25°C (68°F to 77°F) for up to 96 hours (4 days). JELMYTO will

appear as a semisolid gel when stored under these conditions. Protect reconstituted JELMYTO from light.

JELMYTO must be instilled as a chilled solution using a Uroject12 Lever, a Luer Lock syringe, and a ureteral catheter with molded Luer Lock connector. Once chilled at  $-3^{\circ}\text{C}$  to  $5^{\circ}\text{C}$  ( $27^{\circ}\text{F}$  to  $41^{\circ}\text{F}$ ), JELMYTO will convert to a viscous liquid for instillation and is stable for up to 1 additional hour. Reconstituted JELMYTO must be instilled within 1 hour after it is converted to a viscous liquid.

### **3 DOSAGE FORMS AND STRENGTHS**

For pyelocalyceal solution: A kit containing the following:

- Two 40 mg (each) single-dose vials of sterile, lyophilized, grey to greyish-purple, cake or powder of mitomycin for pyelocalyceal solution
- One single-dose vial of 20 mL of sterile, clear, colorless gel with or without bubbles at room temperature or clear, colorless liquid at  $2^{\circ}\text{C}$  to  $8^{\circ}\text{C}$  ( $36^{\circ}\text{F}$  to  $46^{\circ}\text{F}$ ), to be used as a vehicle for reconstitution

### **4 CONTRAINDICATIONS**

JELMYTO is contraindicated in patients with perforation of the bladder or upper urinary tract.

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Ureteric Obstruction**

Ureteric obstruction, including ureteral stenosis and hydronephrosis, occurred in patients receiving JELMYTO.

In the OLYMPUS study, ureteric obstruction was reported in 58% ( $n=41$ ) of patients receiving JELMYTO, including 17% ( $n=12$ ) of patients who experienced Grade 3 obstruction. The median time to first onset was 72 days (range: 15-462). Interventions in the 41 patients experiencing ureteric obstruction included ureteral stent placement (88%), balloon dilatation (29%), and nephroureterectomy (4.9%). In the 36 patients who required ureteral stent placement, the median duration of indwelling stents was 52 days (range: 1-292). Ureteric obstruction did not resolve or resolved with sequelae in 44% ( $n=18$ ) of these patients. Of the 41 patients who experienced ureteric obstruction, 17% ( $n=7$ ) experienced Grades 1-2 increase in serum creatinine.

In the 42 patients who only received JELMYTO during the treatment phase (no maintenance therapy), ureteric obstruction was reported in 40% ( $n=17$ ).

Monitor patients for signs and symptoms of ureteric obstruction, including flank pain, and fever, and for changes in renal function. Patients who experience obstruction may require transient or long-term ureteral stents or alternative procedures. Withhold or permanently discontinue JELMYTO based on the severity of ureteric obstruction.

#### **5.2 Bone Marrow Suppression**

The use of JELMYTO can result in bone marrow suppression, particularly thrombocytopenia and neutropenia. In the OLYMPUS study, Grade 3 thrombocytopenia occurred in three patients, Grade 3

anemia in one patient, and Grade 3 neutropenia in one patient. Gross extravasation of JELMYTO via urinary tract perforation or impaired mucosa was not observed in these patients. The following tests should be obtained prior to each treatment: Platelet count, white blood cell count differential and hemoglobin. Withhold JELMYTO for Grade 2 thrombocytopenia or neutropenia. Permanently discontinue for Grade 3 or greater thrombocytopenia or neutropenia.

### **5.3 Embryo-Fetal Toxicity**

Based on findings in animals and mechanism of action, JELMYTO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of mitomycin resulted in teratogenicity. Advise females of reproductive potential to use effective contraception during treatment with JELMYTO and for 6 months following the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with JELMYTO and for 3 months following the last dose [see *Use in Specific Populations* (8.1, 8.3) and *Clinical Pharmacology* (12.1)].

## **6 ADVERSE REACTIONS**

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Ureteric Obstruction [see *Warnings and Precautions* (5.1)]
- Bone Marrow Suppression [see *Warnings and Precautions* (5.2)]

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice.

The safety of JELMYTO was evaluated in OLYMPUS, an open-label, single-arm study in 71 patients with LG-UTUC [see *Clinical Studies* (14)]. For the 71 patients treated with JELMYTO during the treatment period, the median number of instillations was 6 (range: 3-6). Following initial treatment, 29 patients were treated with up to 11 doses of maintenance instillations, with a median of 6 instillations (range: 0-11).

Serious adverse reactions occurred in 39% of patients who received JELMYTO. Serious adverse reactions in > 3% of patients included ureteric obstruction (including ureteric stenosis and hydronephrosis), flank pain, and urosepsis. Two deaths occurred due to cerebrovascular accident and failure to thrive.

JELMYTO was permanently discontinued due to an adverse reaction in 17 (24%) patients, including 11 patients who discontinued during the treatment phase and 6 who discontinued during the maintenance phase. Adverse reactions resulting in study drug discontinuation of JELMYTO in > 3% of patients who received JELMYTO included ureteric obstruction.

Dosage interruptions due to an adverse reaction occurred in 37% of patients who received JELMYTO. Adverse reactions requiring dosage interruption in > 3% of patients who received JELMYTO included renal dysfunction, ureteric obstruction, urinary tract infection, and flank pain.



The most common adverse reactions ( $\geq 20\%$ ) reported were ureteric obstruction, flank pain, urinary tract infection, hematuria, abdominal pain, fatigue, renal dysfunction, nausea, dysuria, and vomiting.

Table 1 summarizes the adverse reactions in OLYMPUS.

<b>Table 1: Adverse Reactions (<math>\geq 10\%</math> All Grades) in Patients Who Received JELMYTO in OLYMPUS</b>		
<b>Adverse Reaction</b>	<b>JELMYTO* (n=71)</b>	
	<b>All Grades (%)</b>	<b>Grade 3-4 (%)</b>
<b>Renal and urinary disorders</b>		
Ureteric Obstruction <sup>†</sup>	58	17
Ureteric stenosis	44	9
Hydronephrosis	18	6
Urinary tract obstruction	7	1.4
Pelvi-ureteric obstruction	6	1.4
Ureteric obstruction	2.8	1.4
Obstructive uropathy	1.4	0
Flank pain <sup>‡</sup>	41	2.8
Hematuria <sup>§</sup>	34	2.8
Urinary tract infection <sup>¶</sup>	34	4.2
Renal dysfunction <sup>#</sup>	25	2.8
Dysuria	23	0
Pollakiuria	14	0
<b>Gastrointestinal disorders</b>		
Abdominal pain <sup>ᵇ</sup>	28	1.4
Nausea	25	1.4
Vomiting	20	4.2
<b>General disorders and administration site conditions</b>		
Fatigue <sup>ᵇ</sup>	27	1.4
Pyrexia	13	1.4
Chills	11	0
<b>Blood and lymphatic system disorders</b>		
Anemia	14	1.4
<b>Skin and subcutaneous tissue disorders</b>		
Pruritus	13	0
<b>Metabolism and nutrition disorders</b>		
Decreased appetite	10	0
<b>Vascular disorders</b>		
Hypertension	10	4.2

\*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCI CTCAE v5)

<sup>†</sup> Includes hydronephrosis, obstructive uropathy, pelvi-ureteric obstruction, ureteric obstruction, ureteric stenosis, and urinary tract obstruction.

<sup>‡</sup> Includes flank pain and back pain.

<sup>§</sup> Includes hematuria and hemorrhage urinary tract.

<sup>¶</sup> Includes urinary tract infection, pyelonephritis, and urinary tract infection fungal.

<sup>#</sup> Includes renal impairment, acute kidney injury, and renal failure.

<sup>ᵇ</sup> Includes abdominal pain and abdominal pain lower.

<sup>ᵇ</sup> Includes asthenia and fatigue.

Selected clinically relevant adverse reactions in  $< 10\%$  and  $\geq 2\%$  of patients who received JELMYTO in OLYMPUS include urinary tract inflammation, bladder spasm, urosepsis, hypersensitivity, and instillation site pain.

Table 2 summarizes the laboratory abnormalities in OLYMPUS.

**Table 2: Select Laboratory Abnormalities ( $\geq 10\%$ ) Worsening from Baseline in Patients Who Received JELMYTO in OLYMPUS**

Laboratory Abnormality*	JELMYTO	
	All Grades (%)	Grade $\geq 3$ (%)
<b>Hematology</b>		
Anemia	38	0
Lymphopenia	21	2.9
Thrombocytopenia	21	2.8
<b>Chemistry</b>		
Estimated Glomerular Filtration Rate (eGFR) <sup>†</sup>	38	11
Creatinine increased	34	0
Hypoalbuminemia	28	2.8
Hypocalcemia	16	0
Hyperuricemia	16	16
Hyperkalemia	13	1.4
Hypernatremia	11	0

\* Graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5). Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available.

<sup>†</sup> eGFR calculated per MDRD (Modification of Diet in Renal Disease) equation

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on findings in animals and mechanism of action, JELMYTO can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no available data on JELMYTO use in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of mitomycin resulted in teratogenicity (see *Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

#### Data

##### *Animal Data*

Teratological changes have been noted with mitomycin in animal studies.

### 8.2 Lactation

#### Risk Summary

There are no data on the presence of mitomycin in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with JELMYTO and for 1 week following the last dose.

### 8.3 Females and Males of Reproductive Potential

JELMYTO can cause fetal harm when administered to pregnant women [*see Use in Specific Populations (8.1)*].

#### Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating JELMYTO.

#### Contraception

##### *Females*

Advise females of reproductive potential to use effective contraception during treatment with JELMYTO and for 6 months following the last dose.

##### *Males*

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with JELMYTO and for 3 months following the last dose.

### 8.4 Pediatric Use

Safety and efficacy in pediatric patients have not been established.

### 8.5 Geriatric Use

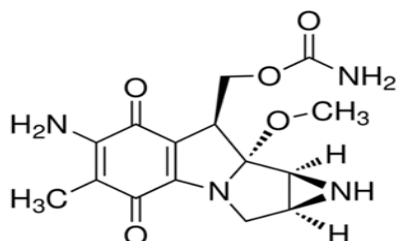
Of the total number of patients in the OLYMPUS trial, 75% (53 patients) were 65 years of age and over and 37% (26 patients) were 75 years of age and over. Clinical studies of JELMYTO did not include sufficient numbers of younger patients less than 65 years old to determine whether they respond differently from older patients.

### 8.6 Renal Impairment

No data are available in patients with severe renal impairment. Avoid use of JELMYTO in patients with a Glomerular Filtration Rate of < 30 mL/min.

## 11 DESCRIPTION

Mitomycin (also known as mitomycin-C) is an alkylating drug isolated from the broth of *Streptomyces caespitosus*. Mitomycin is a blue-violet crystalline powder with a molecular formula of C<sub>15</sub>H<sub>18</sub>N<sub>4</sub>O<sub>5</sub>, and a molecular weight of 334.33. Its chemical name is 7-amino-9 $\alpha$ -methoxymitosane, and it has the following structural formula:



Mitomycin is heat stable, has a high melting point, and is freely soluble in organic solvents.

JELMYTO is supplied in a kit containing two vials of sterile lyophilized mitomycin for pyelocalyceal solution, 40 mg each, and one vial of 20 mL of sterile hydrogel, to be used as a vehicle for reconstitution.

Mitomycin for pyelocalyceal solution is a sterile, lyophilized, grey to greyish-purple, cake or powder that contains mitomycin 40 mg and mannitol 80 mg in each vial.

Sterile hydrogel is a sterile, clear, colorless gel with or without bubbles at room temperature or clear, colorless liquid at 2°C to 8°C (36°F to 46°F), which contains 0.04 g hydroxypropyl methylcellulose, 5.67 g poloxamer, 0.21 g polyethylene glycol, and water for injection in each vial.

Once reconstituted, JELMYTO is a clear, purple, viscous liquid at 2°C to 8°C (36°F to 46°F) or semisolid gel at room temperature with a concentration of 4 mg per mL of mitomycin, which may contain a few visible particles and have a pH between 6.0 and 8.0.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Mitomycin inhibits the synthesis of deoxyribonucleic acid (DNA). The guanine and cytosine content correlates with the degree of mitomycin-induced cross-linking. At high concentrations of the drug, cellular RNA and protein synthesis are also suppressed.

### **12.2 Pharmacodynamics**

There is insufficient data to characterize an exposure-response relationship or time course of pharmacodynamic response for mitomycin.

### **12.3 Pharmacokinetics**

#### Absorption

The systemic exposure of mitomycin following instillation of up to 60 mg of mitomycin as JELMYTO into the pyelocalyceal system was evaluated pre-instillation and hourly for up to six hours post-instillation in six patients. The concentrations of mitomycin in plasma were variable and ranged from 2.43 to 12.80 ng/mL over the course of treatment; the mean  $C_{max}$  was 6.24 ng/mL, which is estimated to be less than 1% of the expected  $C_{max}$  after intravenous administration.

#### Elimination

Following instillation into the pyelocalyceal system, JELMYTO forms a semisolid gel which dissolves from normal kidney urine flow releasing mitomycin for up to 4 to 6 hours. Mitomycin is eliminated unchanged in the urine. Systemically absorbed mitomycin is rapidly cleared from the serum and approximately 10% is excreted unchanged in the urine.



### Metabolism

Mitomycin is metabolized primarily in the liver, but metabolism occurs in other tissues as well. It is believed that the rate of clearance is inversely proportional to the maximal serum concentration because of saturation of the degradative pathways.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Adequate long-term studies in animals to evaluate carcinogenic potential from instillation of mitomycin into the pyelocalyceal system have not been conducted. Mitomycin has been found to be carcinogenic in rats and mice. At doses approximating the recommended intravenous clinical dose in humans, mitomycin produced a greater than 100% increase in tumor incidence in male Sprague-Dawley rats, and a greater than 50% increase in tumor incidence in female Swiss mice.

The effect of JELMYTO on fertility is unknown.

## **14 CLINICAL STUDIES**

The efficacy of JELMYTO is based on the results of the OLYMPUS study (NCT02793128), an open-label, single-arm, multicenter trial that enrolled 71 patients with treatment-naïve or recurrent non-invasive low-grade upper tract urothelial cancer (LG-UTUC) with at least one measurable papillary tumor 5 to  $\leq$  15 mm located above the ureteropelvic junction; patients who had larger tumors could have had tumor debulking prior to treatment, in order to meet the criteria. Patients were excluded from the trial for a history of carcinoma in situ (CIS) in the urinary tract, invasive urothelial carcinoma within 5 years, high grade papillary urothelial carcinoma within 2 years; or for BCG treatment within 6 months of JELMYTO treatment. Following biopsy and prior to treatment, patients were required to have at least one remaining visible tumor with a diameter of at least 5 mm.

Patients received JELMYTO 4 mg per mL via ureteral catheter or nephrostomy tube with total instillation volume based on individualized volumetric measurements using pyelography with the intent to fill the renal pelvis. Patients were treated with 6 instillations once a week. Patients who maintained a complete response (CR) after the initial treatment period were allowed to proceed to the follow-up period. During the initial treatment period, 71 patients were treated with JELMYTO, of whom 41 were subsequently continued in the follow-up period. During the follow-up period, 29 patients received at least one dose of maintenance therapy.

The baseline demographic and disease characteristics for the trial population were: median age 71 years (range: 42-87 years); 68% male; 87% White; 90% Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1 and 10% ECOG PS 2. The median number of papillary lesions subsequent to debulking and/or biopsy and prior to treatment was 1 lesion (range: 1, 5), the median diameter of the largest lesion was 8.0 mm (range: 5.0, 15.0), and the median total visible tumor burden was 10.0 mm (range: 5.0, 25.0). Twenty-six (37%) patients underwent tumor debulking during the six weeks preceding enrollment. Of 71 enrolled patients, 48% had tumors located in regions not amenable to endoscopic resection. General anesthesia was used in 37% of patients for at least one instillation during the treatment period and for 83% of patients for at least one instillation during the follow-up period.

The major efficacy outcome measures were CR and durability of CR at 12 months after determination of CR based on ureteroscopic and local pathology assessment. CR was defined as complete absence of

tumor lesions in the ipsilateral pyelocalyceal system at 3 months after initiation of JELMYTO by urine cytology and ureteroscopy. Biopsy was performed if warranted. Durability of response in patients with a CR was evaluated at 3, 6, 9 and 12 months following the initial assessment. Assessment of durability of CR subsequent to these evaluations was performed per local standards of care.

Forty-one patients (58%) achieved CR in the study (95% CI: 45%, 69%). Of the 41 patients who achieved CR, 23 (56%) of the patients remained at CR at the 12-month time point for assessment of durability, 8 (20%) experienced recurrence of disease, and 10 (24%) were unable to be evaluated (died, discontinued from the study, or were indeterminate for ongoing response). The median duration of response was not reached (range: 0, 18.8 months and ongoing). One patient, who achieved 6 months of durable CR, was diagnosed with metastatic urothelial carcinoma approximately 4.5 months after the last dose of study medication and died from the disease.

## 15 REFERENCES

1. "OSHA Hazardous Drugs." OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

JELMYTO kit – NDC 72493-103-03

JELMYTO is available in a kit containing the following:

- Two 40 mg (each) single-dose vials of mitomycin for pyelocalyceal solution supplied as a sterile, lyophilized, grey to greyish-purple, cake or powder. (NDC 72493-101-40)
- One 20 mL single-dose vial of sterile hydrogel supplied as a sterile, clear, colorless gel with or without bubbles at room temperature or clear, colorless liquid at 2°C to 8°C (36°F to 46°F), to be used as a vehicle for reconstitution. (NDC 72493-102-20)

### 16.2 Storage and Handling

Store the JELMYTO kit at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Avoid excessive heat over 40°C (104°F). Protect from light.

JELMYTO is a hazardous drug. Follow applicable special handling and disposal procedures.<sup>1</sup>

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

### Ureteric Obstruction

Inform patients that ureteric obstruction may occur, and ureteral stents or alternative procedures may be required during treatment with JELMYTO. Advise patients to contact their healthcare provider immediately if signs and symptoms of ureteric obstruction, including flank pain and/or fever, occur [*see Warnings and Precautions (5.1)*].

### Bone Marrow Suppression

Inform patients that JELMYTO may decrease blood counts such as white blood cells and platelets. Thus, it is important that periodic assessment of their blood counts be performed to detect the development of neutropenia and thrombocytopenia [see *Warnings and Precautions* (5.2)].

### Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare providers of a known or suspected pregnancy [see *Warnings and Precautions* (5.3) and *Use in Specific Populations* (8.1)].

Advise females of reproductive potential to use effective contraception during treatment with JELMYTO and for 6 months following the last dose [see *Use in Specific Populations* (8.3)].

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with JELMYTO and for 3 months following the last dose [see *Use in Specific Populations* (8.3)].

### Lactation

Advise women not to breastfeed during treatment with JELMYTO and for 1 week following the last dose [see *Use in Specific Populations* (8.2)].

### Important Post-Treatment Instructions [see *Dosage and Administration* (2.1)]

Advise patients that JELMYTO contains mitomycin which is a violet to blue color and may discolor urine following the instillation procedure.

Advise patients to avoid contact with urine for at least six hours post-instillation.

Advise patients to void sitting on a toilet, flush the toilet several times after use, and to wash hands, perineum or glans with soap and water after each instillation procedure.

Advise patients to wash clothing soiled with urine promptly and separately from other clothing.

Distributed by:

**UroGen Pharma, Inc.**

Princeton, NJ 08540

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U.S. Patent Nos. 9,040,074 and 9,950,069

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JEL-PI-003

**Patient Information**  
**JELMYTO® (jel-MYE-toe)**  
**(mitomycin)**  
**for pyelocalyceal solution**

**What is JELMYTO?**

JELMYTO is a prescription medicine used to treat adults with a type of cancer of the lining of the upper urinary tract including the kidney called low-grade Upper Tract Urothelial Cancer (LG-UTUC).

It is not known if JELMYTO is safe and effective for use in children.

**Who should not receive JELMYTO?**

**Do not receive JELMYTO if you** have a hole or tear (perforation) of your bladder or upper urinary tract.

**Before receiving JELMYTO, tell your healthcare provider about all your medical conditions, including if you:**

- are pregnant or plan to become pregnant. JELMYTO can harm your unborn baby. You should not become pregnant during treatment with JELMYTO. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with JELMYTO.

**Females who are able to become pregnant:**

- Your healthcare provider will check to see if you are pregnant before starting treatment with JELMYTO.
- You should use effective birth control (contraception) during treatment with JELMYTO and for 6 months after the last dose.
- Talk to your healthcare provider if you have questions about birth control options that are right for you.

**Males being treated with JELMYTO:**

- If you have a female partner who is able to become pregnant, you should use effective birth control (contraception) during treatment with JELMYTO and for 3 months after the last dose.
- are breastfeeding or plan to breastfeed. It is not known if JELMYTO passes into your breast milk. Do not breastfeed during treatment with JELMYTO and for 1 week after the last dose.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

**Especially tell your healthcare provider if you take water pills (diuretic).**

**How will I receive JELMYTO?**

- Your healthcare provider will tell you to take a medicine called sodium bicarbonate before each JELMYTO treatment. Your healthcare provider will provide instructions about how and when to take sodium bicarbonate.
- JELMYTO will be given to you by your healthcare provider.
- You will receive JELMYTO 1 time a week for 6 weeks. It is important that you receive all 6 doses of JELMYTO according to your healthcare provider's instructions. Your healthcare provider may recommend up to an additional 11 monthly doses.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.
- JELMYTO is given to your kidney through a tube called a catheter.
- During treatment with JELMYTO, your healthcare provider may tell you to take additional medicines or change how you take your current medicines. Ask your healthcare provider if you have any questions.

**After receiving JELMYTO:**

- JELMYTO may cause your urine color to change to a violet to blue color.
- Avoid contact between your skin and urine for at least 6 hours.
- To urinate, **males and females should sit** on a toilet and flush the toilet several times after you use it.
- After going to the bathroom, wash your hands, your inner thighs, and genital area well with soap and water.
- Clothing that comes in contact with urine should be washed right away and washed separately from other clothing.

**What are the possible side effects of JELMYTO?**

**JELMYTO may cause serious side effects, including:**

- **Swelling and narrowing of the tube that carries urine from the kidney to the bladder (ureteric obstruction).** If you develop swelling and narrowing, and to protect your kidney from damage, your healthcare provider may recommend the placement of a small plastic tube (stent) in the ureter to help the kidney drain. Tell your healthcare provider right away if you develop side pain or fever during treatment with JELMYTO.



- **Bone marrow problems.** JELMYTO can affect your bone marrow and can cause a decrease in your white blood cell, red blood cell, and platelet counts. Your healthcare provider will do blood tests prior to each treatment to check your blood cell counts during treatment with JELMYTO. Your healthcare provider may need to temporarily or permanently stop JELMYTO if you develop bone marrow problems during treatment with JELMYTO.

**The most common side effects of JELMYTO include:**

- urinary tract infection
- blood in your urine
- side pain
- nausea
- trouble with urination
- kidney problems
- vomiting
- tiredness
- stomach (abdomen) pain

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You can also report side effects to UroGen Pharma at 1-855-987-6436.

**General information about JELMYTO.**

Medicines are sometimes prescribed for purposes other than those listed in this Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about JELMYTO that is written for healthcare professionals.

**What are the ingredients of JELMYTO?**

**Active ingredient:** mitomycin

**Inactive ingredients:** hydroxypropyl methylcellulose, mannitol, poloxamer, polyethylene glycol, and water for injection

Distributed by:

**UroGen Pharma, Inc.**

Princeton, NJ 08540

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U.S. Patent Nos. 9,040,074 and 9,950,069

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JEL-PPI-003

For more information go to [www.JELMYTO.com](http://www.JELMYTO.com) or call 1-855-987-6436.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: 09/2022

# **INSTRUCTIONS FOR PHARMACY (IFP) JELMYTO® (jel-MYE-toe) (mitomycin) for pyelocalyceal solution**

## **Purpose of this Instructions for Pharmacy**

This Instructions for Pharmacy contains information on how to prepare JELMYTO using pharmacy supplies and a Chilling Block.

## **Intended Use of JELMYTO**

JELMYTO (mitomycin) for pyelocalyceal solution is indicated for the treatment of adult patients with low-grade Upper Tract Urothelial Cancer (LG-UTUC).

## **Important Information You Need to Know Before Reconstituting JELMYTO**

Once reconstituted with sterile hydrogel, JELMYTO will appear as a semisolid gel. Once chilled, JELMYTO will convert to a viscous liquid.

Reconstituted JELMYTO must be prepared under chilled conditions. A Chilling Block can be used for this purpose. JELMYTO cannot be prepared without the Chilling Block or other means of chilling.


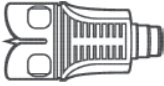
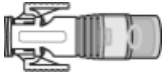
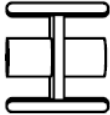

Preparation of JELMYTO must be performed under aseptic conditions.

## **Storage Conditions and Handling**

Instill the JELMYTO solution as soon as possible after reconstitution. Store reconstituted JELMYTO at 20°C to 25°C (68°F to 77°F) for up to 96 hours (4 days). Protect from light.

JELMYTO is a cytotoxic anti-cancer drug. Procedures for Proper Handling and Disposal of anti-cancer drugs should be followed.

## Supplies Needed:

<p><b>JELMYTO Kit containing:</b></p> <ul style="list-style-type: none"> <li>• 2 Vials of Mitomycin for Pyelocalyceal Solution, 40 mg/vial</li> <li>• 1 Vial Sterile Hydrogel, 20 mL/vial</li> <li>• 1 JELMYTO Admixture Label</li> <li>• JELMYTO Full Prescribing Information (PI)</li> <li>• JELMYTO Instructions for Pharmacy (IFP)</li> <li>• JELMYTO Instructions for Administration (IFA)</li> </ul>	
<p><b>Pharmacy Supplies</b> (Provided by Your Facility)</p> <p><b>Do not substitute any of these components.</b></p> <ul style="list-style-type: none"> <li>• 3 x TEVADAPTOR® or OnGuard®2 CSTD Vial Adaptors</li> <li>• 3 x TEVADAPTOR® or OnGuard®2 CSTD Syringe Adaptors</li> <li>• 1 x Luer Lock connector</li> <li>• 2 x 10 mL Luer Lock syringes</li> <li>• 1 x 20 mL Luer Lock syringe</li> <li>• 1 x 20-25G needle (for drawing up sterile water)</li> <li>• 2 mL sterile water</li> <li>• 70% Isopropyl alcohol or equivalent</li> <li>• 1 x Light protective bag</li> <li>• 1 x Chilling Block (device design may vary)</li> </ul> <p><b>Note:</b> The day before your preparation, put the Chilling Block in the freezer at -20°C to -12°C (-4°F to 10.4°F) overnight. Please refer to the Chilling Block Instructions for Use for more information.</p>	 <p>3 x TEVADAPTOR® or OnGuard®2 CSTD Vial Adaptors</p>  <p>3 x TEVADAPTOR® or OnGuard®2 CSTD Syringe Adaptors</p>  <p>1 x Luer Lock connector</p>  <p>1 x Chilling Block</p>

## Steps to Prepare JELMYTO Admixture

### A. Freeze Chilling Block

The day before preparation, put the Chilling Block in the freezer at -20°C to -12°C (-4°F to 10.4°F) overnight.

**Note:** Please refer to the Chilling Block Instructions for Use for additional information.

### B. Prepare Supplies

1. Remove the Chilling Block from the freezer.
2. Disinfect the Chilling Block with 70% Isopropyl alcohol or equivalent, as per your pharmacy's policy. Allow it to air dry, and then place it upright inside the hood or isolator.
3. Wait 20 minutes before continuing.
4. Connect vial adaptors to all three vials.
5. Connect a syringe adaptor to one of the 10 mL syringes.
6. Connect a syringe adaptor to the 20 mL syringe.
7. Place the three vials, the 10 mL syringe, and the 20 mL syringe into the Chilling Block for at least 10 minutes.
8. While the vials and syringes are in the Chilling Block, withdraw 2 mL of sterile water into the other 10 mL syringe and set aside for later use.

### C. Create Pre-Wetting Solution (PWS)

1. Slowly fill the chilled 20 mL syringe with 14 mL of sterile hydrogel.
2. Recap the chilled 20 mL syringe and place it in the Chilling Block.
3. Slowly fill the chilled 10 mL syringe with 4 mL of sterile hydrogel.
4. Discard the unused portion of sterile hydrogel.
5. Replace the needle on 2 mL sterile water syringe with the Luer Lock connector.
6. Remove the syringe adaptor from the 4 mL sterile hydrogel syringe.



7. Connect the 4 mL sterile hydrogel syringe to the other side of the Luer Lock connector on the 2 mL sterile water syringe.
8. Gently mix the sterile water with the sterile hydrogel by pushing the plungers back and forth at least 25 times to create the “pre-wetting solution” (PWS).
9. Transfer the 6 mL PWS into one of the syringes.
10. Replace the Luer Lock connector on the 6 mL PWS syringe with a new syringe adaptor.
11. Place the 6 mL PWS syringe in the Chilling Block.

#### **D. Mix the Admixture**

1. Remove both JELMYTO vials from the Chilling Block.
2. Gently tap the bottom of each vial on the table to ensure all the mitomycin powder is at the bottom of the vials.
3. Remove the chilled 6 mL PWS syringe from the Chilling Block.
4. Inject 3 mL of PWS into each JELMYTO vial.  
**Note:** To ensure accurate dosing, the contents of each vial must be the same.
5. Discard the empty PWS syringe.
6. Gently swirl each JELMYTO vial upright at least 15 times, ensuring all powder and admixture is contained at the bottom of the vial.  
**Note:** Do not invert or shake the vials.
7. Immediately remove the chilled 14 mL sterile hydrogel syringe from the Chilling Block.
8. Immediately inject 7 mL of sterile hydrogel into each JELMYTO vial.  
**Note:** To ensure accurate dosing, the contents of each vial must be the same.
9. Gently swirl each JELMYTO vial upright at least 15 times, ensuring all admixture is contained at the bottom of the vial.  
**Note:** Do not invert or shake the vials.
10. Recap and place the 20 mL syringe in the Chilling Block.
11. Mix the JELMYTO admixture vials:
  - Recap and place both JELMYTO vials in the Chilling Block for **five minutes**.

- Remove both vials and vigorously swirl them upright at least 15 times, ensuring all admixture is contained at the bottom of the vials.
- Place both vials back in the Chilling Block.
- **Repeat these steps every five minutes for a total of 30 minutes.**

**Note:** Do not invert or shake the vials.

#### **E. Prepare Admixture Vial**

1. Remove one JELMYTO vial from the Chilling Block.
2. Vigorously swirl the vial upright at least 15 times.  
**Note:** Do not invert or shake the vial.
3. Using the chilled 20 mL syringe, slowly withdraw 7 mL of admixture from the vial.  
**Note:** If you are having difficulty withdrawing the admixture, place the components back in the Chilling Block until the admixture liquifies again.
4. Discard the empty JELMYTO vial.
5. Remove the remaining JELMYTO vial from the Chilling Block.
6. Inject the contents of the 20 mL syringe into that vial. Now all the admixture is contained in one vial.
7. Recap the vial adaptor.
8. Vigorously swirl the vial upright at least 15 times.  
**Note:** Do not invert or shake the vial.
9. Your JELMYTO admixture vial is now complete, with a resultant concentration of 4 mg of mitomycin per mL following reconstitution.

#### **F. Dispense Admixture Vial**



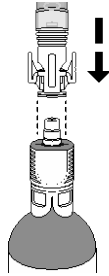
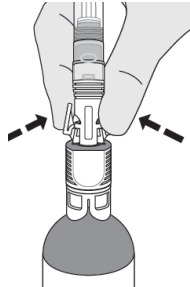
1. Write the “Discard after” date and time on the supplied admixture label and apply to the prepared JELMYTO admixture vial. You may also substitute your pharmacy’s label for dispensing the admixture.  
**Note:** The “Discard after” date and time is 96 hours (4 days) from the completion of the preparation at room temperature.
2. Place the JELMYTO admixture vial in a light-protective bag.
3. Transport to the treatment facility along with the JELMYTO Instructions for Administration.



## Important to Remember

- All components must be kept cold during the preparation process by placing them in the Chilling Block when they are not in use.
- If you have difficulty pushing the solution or withdrawing the solution at any time, put the components back in the Chilling Block until the product liquifies.

## Frequently Asked Questions:

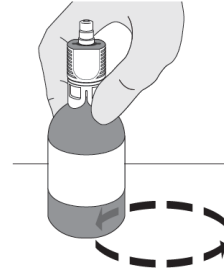
<p><b>How do I connect the vial adaptor?</b></p> <p>Place the vial adaptor over the vial and press down firmly. You will hear a snap which confirms successful attachment.</p>	
<p><b>How do I connect the syringe adaptor?</b></p> <p>Screw the Luer Lock end of the syringe adaptor onto the syringe hub until it is finger tight.</p>	
<p><b>How do I connect the syringe adaptor to the vial adaptor?</b></p> <p>Place the syringe adaptor over the vial adaptor and align the tabs, then press down firmly. You will hear a snap which confirms successful attachment.</p>	
<p><b>How do I disconnect the syringe adaptor from the vial adaptor?</b></p> <p>Pinch the tabs on the syringe adaptor to separate it from the vial adaptor.</p>	

**Do I need to put the caps on the syringes and vials before placing them back into the chilling block?**

YES, the chilling block inserts are not sterile. It is important to maintain aseptic technique.

**Do I have to keep the vials upright when mixing? If so, why?**

YES, the vials should be upright during all mixing to ensure the contents are fully mixed at the bottom of the vial.



**I am having difficulty working with the drug product. It seems to be solidifying.**

If you are having difficulty pushing the solution or withdrawing the solution, place the components back into the Chilling Block until the product liquifies.

This “Instructions for Pharmacy” has been approved by the U.S. Food and Drug Administration.

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JEL-IFP-003

IFP-0002025/Ver. 4

# **INSTRUCTIONS FOR ADMINISTRATION (IFA)**

## **JELMYTO® (jel-MYE-toe)**

### **(mitomycin) for pyelocalyceal solution**

### **For Pyelocalyceal Instillation Only**



**Read and follow this Instructions for Administration prior to each JELMYTO instillation.**

## **Purpose of this Instructions for Administration**

This Instructions for Administration contains information on how to instill JELMYTO using the reconstituted JELMYTO vial which you received from the pharmacy and the devices listed under **Supplies Needed**, obtained by your facility.

## **Intended Use of JELMYTO**

JELMYTO (mitomycin) for pyelocalyceal solution is indicated for the treatment of adult patients with low-grade Upper Tract Urothelial Cancer (LG-UTUC).

## **Important Information You Need to Know Before Instilling JELMYTO**

JELMYTO must be reconstituted by a healthcare professional prior to instillation. Reconstituted JELMYTO will appear as a semisolid gel. Once chilled, JELMYTO will convert to a viscous liquid for instillation.

Once instilled into the patient's pyelocalyceal system, JELMYTO will fill and conform to the cavity and become a gel, thereby exposing the tissue to mitomycin over a prolonged period of time.

JELMYTO is viscous, even when it is a liquid in a chilled state. Therefore, you will need a Uroject12 Syringe Lever to instill JELMYTO into the patient. You cannot instill JELMYTO without the Uroject12 device.

Reconstituted JELMYTO should be instilled as soon as possible after reconstitution. Store reconstituted JELMYTO at 20°C to 25°C (68°F to 77°F) for up to 96 hours (4 days). Protect from light.

**When ready to instill, chill JELMYTO to 27°F to 41°F (-3°C to 5°C) for at least 10 minutes, but no longer than one hour, to revert it to a liquid form. See the Steps A through E for complete administration instructions.**

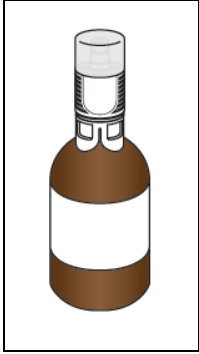
JELMYTO is a cytotoxic anti-cancer drug. Procedures for Proper Handling and Disposal of anti-cancer drugs should be followed.



## Supplies Needed:

**One vial of reconstituted JELMYTO, with a resultant concentration of 4 mg of mitomycin per mL following reconstitution.**

(prepared and provided by the pharmacy)



JELMYTO vial

## **Ancillary Supplies:**

(to be provided by your facility)



**Do not substitute any of these components.**

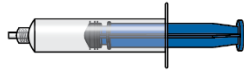
- TEVADAPTOR® Syringe Adaptor or OnGuard®2 CSTD Syringe Adaptor
- MEDALLION® COP or MEDALLION® Luer Lock syringe, 20 mL
- Ureteral Catheter with molded Luer lock port (5 Fr or 7 Fr)
- Uroject12 Syringe Lever

**Note:** The Uroject12 Syringe Lever is a multi-use device and must be sterilized or disinfected before use. Please follow the sterilization or disinfection instructions detailed in the Uroject12 Syringe Lever Instructions for Use.

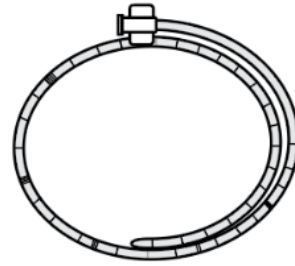
- An ice bath to chill the vial of JELMYTO prior to instillation.



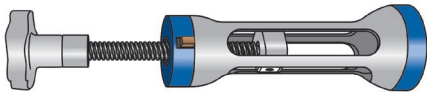
**TEVADAPTOR® or  
OnGuard®2 CSTD Syringe  
Adaptor**



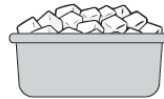
**MEDALLION® COP or  
MEDALLION® Luer Lock  
syringe, 20 mL**



**Ureteral Catheter with  
molded Luer lock port**



**Uroject12 Syringe Lever**



**Ice Bath**

## Instillation Instructions

### A. Measure the Kidney Volume

The Instillation Volume will be equal to the patient's kidney volume. If the kidney volume is already known, proceed to Section B.

If the kidney volume is NOT known, or needs to be reassessed, use the following steps:

1. Perform a retrograde pyelogram using diluted contrast (50%) so that the entire renal pelvis and calyces are observed and contrast starts to flow below the ureteropelvic junction (UPJ).
2. Record the volume of contrast injected at this point.
3. Allow the contrast to drain from the kidney. This may take about five minutes.  
**Note:** Do not withdraw contrast back into the syringe.
4. Repeat Steps 1 through 3 two more times, for a total of three measurements to improve accuracy.
5. Average the three volume measurements and round to the nearest whole number. This is the patient's kidney volume.

**B. Select the Instillation Volume**

Select the kidney volume OR 15 mL, **whichever is lower**, as the Instillation Volume.

**Note: Maximum Instillation Volume is 15 mL.** Record this volume for future instillations.

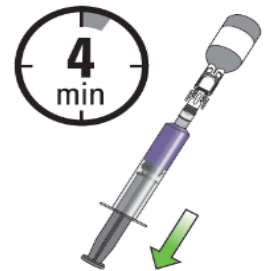
**C. Chill the JELMYTO**

1. Place the JELMYTO vial in the ice bath for at least 10 minutes, but no longer than one hour.
2. After at least 10 minutes, advance the ureteral catheter over the guidewire towards the target anatomy in the pyelocalyceal system.

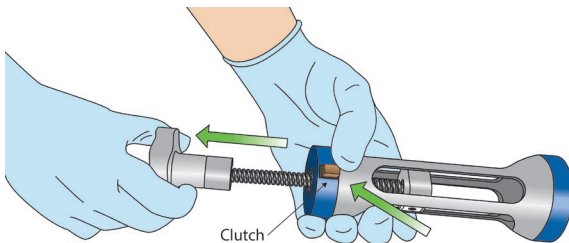
**D. Prepare the Administration Syringe**

Once the vial is removed from the ice bath, **you have 4 minutes to draw JELMYTO into the administration syringe** before it solidifies.

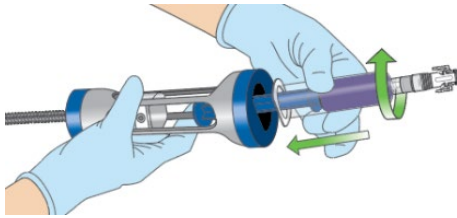
After 4 minutes, recap and place the components back in the ice bath for no more than 15 minutes to liquify the JELMYTO.



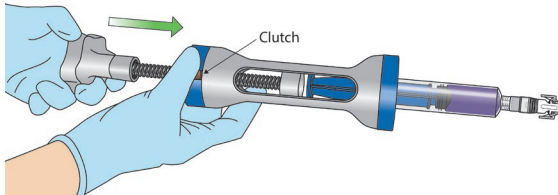
1. Remove the JELMYTO vial from the ice bath and dry it off.
2. Swirl the vial upright to ensure that JELMYTO is uniformly mixed.
3. Connect the syringe adaptor to the 20 mL Luer Lock syringe. This will be the administration syringe.
4. Slowly withdraw the calculated Instillation Volume of JELMYTO into the administration syringe.
5. Press the "Clutch" button on the Uroject12 and pull the knob out.



6. Insert the administration syringe into the Uroject12 Syringe Lever and rotate it clockwise until it locks in place.



7. While pressing the “Clutch” button, advance the lever to just above the administration syringe’s plunger.



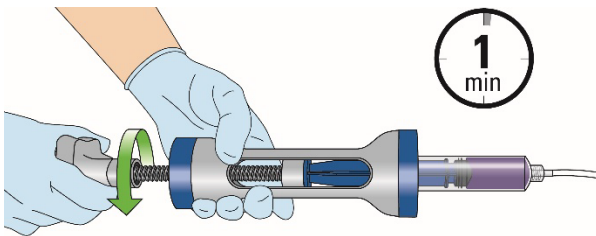
Immediately proceed with the instillation steps in Section E to avoid JELMYTO solidification.

#### E. Instill JELMYTO

1. Remove the syringe adaptor from the administration syringe.

**Note:** If JELMYTO gets on to the syringe tip or the catheter’s Luer Lock port, wipe it off immediately with sterile gauze so it does not solidify and prevent a secure connection. (Refer to **Frequently Asked Questions** for further details.)

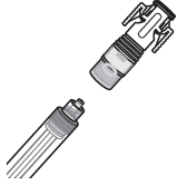
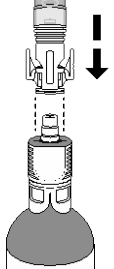
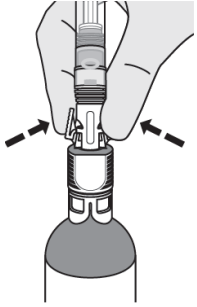
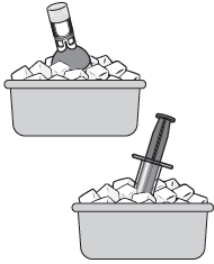
2. Connect the administration syringe to the ureteral catheter’s Luer Lock port, by rotating the syringe only.
3. Using fluoroscopy, ensure the ureteral catheter is in the desired anatomical position.
4. Gradually instill the JELMYTO into the patient by turning the knob at a rate of 1-2 seconds per stroke. **The entire syringe must be emptied within one minute.**



5. Remove the ureteral catheter from the urinary tract.

6. Remove the administration syringe from the Uroject12 by rotating the syringe barrel counter-clockwise.
7. Discard the administration ancillaries according to your facility's disposal procedures.
8. Send the Uroject12 to be reprocessed according to your facility's procedures and the Uroject12 Syringe Lever Instructions for Use.

## Frequently Asked Questions:

<p><b>How do I connect the syringe adaptor?</b></p> <p>Screw the Luer Lock end of the syringe adaptor onto the syringe hub until it is finger tight.</p>	
<p><b>How do I connect the syringe adaptor to the vial adaptor?</b></p> <p>Place the syringe adaptor over the vial adaptor and align the tabs; then press down firmly. You will hear a snap which confirms successful attachment.</p>	
<p><b>How do I disconnect the syringe adaptor from the vial adaptor?</b></p> <p>Pinch the tabs on the syringe adaptor to separate it from the vial adaptor.</p>	
<p><b>I am having a hard time working with reconstituted JELMYTO. It seems to be solidifying.</b></p> <p>If you are having difficulty pushing or withdrawing JELMYTO, recap and place the components back into the ice bath until JELMYTO liquifies.</p>	



### What should I do if there is JELMYTO spillage from the syringe tip?

You will need to clean JELMYTO off the syringe tip and the Luer Lock port of the catheter to ensure the two components can connect securely.

- To clean the syringe tip, fold a sterile gauze pad in half twice, and push it into the inside of the Luer Lock port to wipe any JELMYTO off the threads.
- To clean the Luer Lock port on the catheter, use a sterile gauze pad to wipe off any JELMYTO.

Verify that the connectors are clean to ensure a secure connection between the syringe and the catheter.



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IFU-Phy-0006722/Ver. 5